HERITAGE UNIVERSITY
INSTITUTIONAL REVIEW BOARD (IRB)
PROTOCOL & PROCEDURE MANUAL
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CHAPTER 1: INTRODUCTION

I. Ethical Principles in Research; Role of IRB

Heritage University's Institutional Review Board (IRB) has institutional responsibility for all use of human subjects under the auspices of, or utilizing the students, personnel or facilities of, Heritage University. All research projects must be accomplished in accord with this policy, and all research projects covered by this policy may be undertaken only after appropriate approval and may continue only so long as that approval remains in effect.

Heritage University recognizes, and affirms, the need for academic freedom in the conduct of research, and the value of well-designed, responsible activities that involve human subjects. At the same time, Heritage University recognizes and accepts its responsibility to assure the protection of any human subjects involved in research. It is the policy of Heritage University to adhere to the generally accepted ethical and professional standards for the protection of human subjects of research that are described in The Belmont Report, the Declaration of Helsinki, and the Nuremberg Code. The three Belmont Principles have been summarized by the Office for Protection from Research Risks, National Institutes of Health, as follows:

1. "Respect for Persons involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy….Required by the moral principle of respect for persons, informed consent contains three elements: information, comprehension, and voluntariness…Institutional Review Boards (IRB) should be especially sensitive to these factors when particularly vulnerable subjects are involved."
2. "Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks or harm…The Report recommends the Institutional Review Board's insistence upon precise answers to direct questions. The IRB should:
    a. Determine the 'validity of the presuppositions of the research'
    b. Distinguish the 'nature, probability, and magnitude of risk with as much clarity as possible,' and
    c. 'determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judges by known facts or other available studies.'
3. "Justice requires that the benefits and burdens of research be distributed fairly. The principles of justice mandate that the selection of research subjects must be the result of fair selection procedures and must also result in fair selection outcomes. The 'justness' of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups."

II. Applicability of Policies & Procedures

The Authorized Institutional Official (AIO) is charged with the responsibility of protecting human participants in research. The AIO empowers the IRB to suspend or terminate any study previously approved by the IRB or to require additional reviews. Suspension or termination may be due to serious and/or unexpected increased risks to

participants, or continuing or serious noncompliance of the investigator(s) or other factors that the IRB deems warrant suspension or termination. The AIO cannot influence the decision of the IRB or approve a study that has not been approved by the IRB. The AIO also empowers the IRB to create and implement policy that will serve to protect human participants.

The authority to create, change and implement policy is shared by the IRB and AIO. New policies or changes to policies may be presented to the IRB to solicit input from the committee members. At the discretion of the IRB, input may also be sought from those parties that would be affected by the policy.

The AIO at HU may elect to rely on the IRB of other institutions for review and approval of a study. In order to do so, that IRB must be officially designated on HU's Federalwide Assurance and a written agreement must be in place between the two institutions. This is generally used when a study involves HU and a facility with which a close working relationship exists. In such an event, the IRB of the other institution, referred to as the IRB of Record, holds the same rights, authority, and responsibility as the IRB of HU. The President or Provost are designees of the AIO to sign these documents.

Every three years, the AIO and IRB will review all policies that are posted on its website, regardless of the date on which the policy was implemented. Such review will include an assessment of the accuracy and relevancy of the policies, a determination as to whether the policies are in-line with institutional policies and whether there is a need for new policies to be developed. Within this document and posted on the IRB website, if an individual policy has been revised, it will show a revision date.

The institution provides support to the IRB and the IRB members in terms of staffing, office space and an operating budget, including educational opportunities. The AIO reviews the ORB/IRB budget annually with the IRB to ensure adequate resources continue to be available.

It is the policy of Heritage University (HU) that all research involving human participants conducted by the faculty, students and staff of HU, or research conducted using HU facilities, is conducted in accordance with federal regulations, regardless of the funding source. Those regulations include, but are not limited to, the following: 1) Code of Federal Regulations, Title 45 Public Welfare, Department of Health and Human Services, National Institutes of Health Office for Protection from Research Risks, Part 46, Protection of Human Participants; 2) Code of Federal Regulations, 21 CFR 50, 56, 312, 812, as established by the Food and Drug Administration.

Per 45 CFR 46.103, because Heritage University is engaged in human subjects research (not otherwise exempt) that may be conducted or supported by an agency of the U.S. Department of Health and Human Services (HHS), Heritage University has an Office of Human Research Protections (OHRP)-approved Federalwide Assurance (FWA) whereby the University agrees to conduct all human subjects research in compliance with the HHS regulations. The Heritage University FWA number is FWA00009054.

CHAPTER 2: DEFINITION OF RESEARCH

Per 45 CFR 46.102, *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

In some cases, the HU IRB must review pilot research and protocol development, including but not limited to the following activities:

- Development and testing of instruments or measures on human subjects* (even if it is just one subject);
- Testing of research procedures on human subjects*;
- Procedures done on human subjects* for the purpose of refining research design.
- Data collected that will be used solely or in combination with other data for purposes of publication, reports or presentation;
- Development and testing procedures on human subjects* involving needles, catheters, radiation, drugs or devices that are swallowed or inserted in an orifice require IRB approval.

*Please note that the Office for Human Research Protections (OHRP) considers the Principal Investigator as well as all research personnel to be human subjects if testing procedures are to be conducted on them. Therefore, even when pilot tests are conducted on study personnel, the protocol must be reviewed and approved by the IRB prior to initiation.

Pilot studies should be identified as such in applications to the IRB. The informed consent process must explain to subjects that the research is a pilot study.
Procedures that are not considered to be pilot research and do not need to be reviewed by the IRB include, but may not be limited to, the following:

- Training programs designed to teach proven methods that will be used during the conduct of research (i.e., blood drawing training, interview techniques training);
- Refining data collection procedures or preparation of an instrument, such as a survey. For instance, "How could this survey question be misunderstood?", or "In what order should survey instruments be distributed?" This type of study development does not contribute to generalizable knowledge, and therefore is not considered research and does not require IRB review. Such data cannot be used in publications or reports.

CHAPTER 3: RESEARCH RISKS & LEVELS OF IRB REVIEW

IRB approval must be obtained prior to initiating any research activity that meets either the DHHS definition of research involving human participants or the FDA definition of clinical investigation involving human participants and prior to implementing amendments to previously approved research (except when necessary to eliminate apparent immediate hazards to participants). However, HU Faculty and Staff do not have the authority to determine whether human subjects activity needs IRB review. The IRB will publish submission deadlines for studies requiring review by the full convened board at the start of each semester. New submissions requesting expedited review or exempt status can be submitted at any time and are reviewed on an on-going basis.

All forms required for an IRB submission are available on the IRB website. The PI is responsible for submitting complete forms and required supporting documentation. The PI must sign all submissions. Students are required to sign the submission when the research is student initiated (research is related to the doctoral dissertation or master's degree). The signature of the Department Head or Dean is required for all submissions unless the research is funded by an external grant or contract. The signature of the medical monitor is required for interventional studies that are monitored by a physician. The IRB staff and reviewer reserve the right to return any submission that is incomplete or on out-dated forms.

I. Determining the Level of IRB Review

Investigators make an initial determination for which type of review is appropriate for their study (full board, expedited, or exempt) and submit the required number of copies of the protocol and supporting documentation. Upon receipt, the IRB Chair or IRB staff member screens the protocol to verify the PI's initial determination. The protocol is then placed into the appropriate queue for review. The Chair, or his/her designee, makes the final determination of the type of review required and the appropriate expedited or exempt category.

II. When Submission to the IRB is Required

A protocol application must be submitted to the IRB for any study for which research is the intent and the researcher proposes to use or involve any of the following:

- identifiable data collected for non-research purposes (e.g., academic or medical records);
- interaction (communication or interpersonal contact between investigator and participant) through interviews, surveys, and other forms of communication;
- intervention (physical procedures by which data are gathered and manipulations of the participant or the participant's environment that are performed for research purposes);
- student research projects conducted as part of Research Methods Courses;
- access to medical records and data through the medical information systems;
- pathological specimens (directly identifiable or identifiable via codes);
- diagnostic specimens (directly identifiable or identifiable via codes).

The IRB reviews projects when the research:

- is sponsored by the institution;
- is conducted by or under the direction of an employee or agent of the institution in relation to his/her institutional responsibilities;
- is conducted by or under the direction of an employee or agent of the institution using resources of the institution; or
- involves the use of the institution's non-public information (i.e. alumni, students, staff, etc.) to identify or contact human research participants or prospective participants.

The IRB Chair, IRB member, or IRB staff (acting as a designee of the Chair), may determine if a proposed project using human materials/data constitutes human participant research. Investigators are encouraged to submit their proposed project to the IRB using the IRB-5 Request for Exemption from Continuing Review protocol form. The form will be reviewed and a final determination will be made as to whether a study meets the definitions of human participant research set forth in 45 CFR 46.102(d)(f). If the determination is that the project does not constitute human participant research, a letter of determination will be sent to the investigator and the IRB will have no further involvement. If the determination is that the research does involve human participants, the IRB-5 will be reviewed and approved in accordance with the exemption process described above. An IRB-1 application may be required if the research project does not qualify for exempt status. The IRB staff will send a written determination regarding the proposed project to the PI.

III. Exempt Research

Federal regulations allow six specific categories of human participant research to be exempt from continuing IRB review. Although these six categories do involve research with human participants, the research does not expose participating participants to psychological, social or physical risks. Per 45 CFR 46.101(b), the exempt research categories are:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
    a. information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and
    b. any disclosure of the human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
    a. the human participants are elected or appointed public officials or candidates for public office; or
    b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants.
5. Research and demonstration projects which are conducted by or participant to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. procedures for obtaining benefits or services under those programs;
    c. possible changes in or alternatives to those programs or procedures;
    d. or possible changes in methods or levels of payment for benefits or services under those programs
6. Taste and food quality evaluation and consumer acceptance studies,
    a. if wholesome foods without additives are consumed or
    b. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Category 4 applies to retrospective studies of specimens and/or data that have already been collected. The materials must be "on the shelf" (or in the freezer) at the time the protocol is submitted to the IRB. Research that involves the ongoing collection of the specimens and/or data does not meet the criteria for category 4. Category 5 pertains only to studies sponsored or funded by DHHS. Research participant to FDA regulations does not qualify for exemption categories 1 – 5.

Per 45 CFR 46.101(i), the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. Also, the exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

In addition, although not required by regulations, IRB polices and procedures do not allow exemption of most research involving deception, audio or video taping, or HIV+ individuals.

IV. Expedited Review

Federal regulations allow nine specific categories of human participant research to be reviewed through an Expedited Review Procedure. Per 45 CFR 46.110 and 21 CFR 56.110, the research should present no more than minimal risk to human participants and involve only procedures listed in one or more of the following categories:

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 stick, heel stick, ear stick, or venipuncture as follows:
    a. From healthy, nonpregnant adults who weigh at least 110 pounds. For these participants, 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 participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, 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 nondisfiguring 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 gumbase 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 participant or an invasion of the participant'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 nonresearch 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 participants. 45 CFR 46.101(b)(4). 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 participants 45 CFR 46.101 (b)(2) and (b)(3). This listing refers only to research that is not exempt.)
8. 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 participants; (ii) all participants have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of participants; or
    b. Where no participants 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.

V. Research Requiring Full IRB Review

Proposed research that does not qualify for either exempt status or expedited review will be sent to the convened board for full review.

CHAPTER 4: CRITERIA FOR IRB APPROVAL OF PROTOCOLS

I. General Guidelines - Federal & State Regulations

A. Basic Approval Requirements

In order to grant approval to a research study, the IRB must find and document that the following criteria are met, per 45 CFR 46.116(a)(b), at the time of initial approval and sustained through continuing review and requests for an amendment:

- risks to participants are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk, and (ii) whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes;
- risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies participants would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility;
- selection of participants is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons. For example vulnerable populations in proposed studies selected as populations of convenience is not acceptable;
- informed consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with, and to the extent required by regulations (or a request to waive or alter the elements of consent must be approved);
- informed consent will be appropriately documented, in accordance with, and to the extent required by regulations (refer to informed consent section);
- when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants (refer to data safety monitoring section); and
- when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data (this criterion applies to all studies).
- when some or all of the participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these participants.
- when biomedical research procedures are included in a research study, the IRB requires that information be provided by the PI that documents the specific

training/credentials for each individual identified as key personnel that qualifies them to perform each procedure.

B. Other Approvals

Research approved by the IRB may be subject to further appropriate review and approval or disapproval by HU officials. However, those officials may not approve the research if it has not been approved by the IRB [45 CFR 46.112].

II. Informed Consent

A. Elements of Informed Consent

The informed consent process is an interaction between the prospective participant and the PI, co-investigator and/or designated qualified personnel, during which a research study is explained to the participant. The purpose is to ensure that the participant understands the study (purpose, risks, benefits) in which s/he may enroll. The process must allow the participant sufficient time to ask questions and to consider whether to participate. The process must also be conducted in a setting that affords sufficient privacy to the potential participant. The informed consent process is most often documented by use of an IRB approved and validated informed consent form.

At the outset of the consent process, the PI or designated individual authorized to obtain consent should ask the participant if any special provisions are required by them for the consent process. For example, hearing impaired individuals may want a sign language interpreter present or individuals with dyslexia may prefer to have the document read to them.

Consent must be obtained prior to any involvement of the participant in a study. All consent forms must include instructions for the participants as to whom to contact regarding research related questions, research related injuries (if applicable) and how to contact the IRB regarding their rights as a research participant.
In general, participants must consent to any screening procedures as well as to participation in the study. The PI may choose to use two different forms or to use one form encompassing both elements. Participants are considered enrolled at the time of signing the consent form. Participants must be informed that they may be withdrawn if it is determined that they do not meet inclusion criteria. Participants who did not meet the screening criteria are to be reported as withdrawals from the study at the time of continuation.

Exceptions to obtaining consent prior to screening may be made, e.g., if the screening is done through a phone call that the participant initiates and that does not involve extensive or intrusive questions. During the screening process identifiable information should not be recorded 1) until after a participant signs an informed consent form, and HIPAA Authorization, if applicable, or 2) without an IRB-approved partial waiver of the requirement to obtain consent, and a waiver of HIPAA Authorization, if applicable.
In addition to the required elements of consent, the top of the first page of the consent document must indicate the name of the PI, the name(s) of student investigators, the title of the research study (abbreviated title is permissible if approved by the IRB). The form

must leave a one inch margin at the bottom for IRB approval stamps. Researchers are encouraged to use the IRB's consent form template, however, deviations from this format are allowed on a case by case basis in order to best suit the individual research study (i.e., use of a consent form in the format of a letter to an individual). The PI must explain why the standard template is not suited to the study in the protocol application.

Informed consent is an on-going process and the investigator and/or study personnel must keep participants apprised of any developments that may affect their willingness to continue to participate.

The informed consent form is submitted as part of the IRB application. The consent form must contain a signature and date line for the participant (or the legally authorized representative) and for the person obtaining consent. Unless specifically required by the IRB, witnessing of consent is optional. The IRB may also determine whether assent is required and if so how it shall be obtained and/or documented.

Upon approval, an informed consent form will be stamped with the date of IRB approval and the date through which the approval is valid. The PI and study personnel are required to use copies of the most recently approved and stamped IRB forms when obtaining consent. The participant must be provided with a copy of the IRB approved document that has been signed and dated by the participant (or legally authorized representative) and the person obtaining consent. The PI should also keep one copy of the consent form. Investigators are required to keep consent forms on file for 3 years following the completion of the research (refer to Record Retention section).

Except as subsequently noted, informed consent will be sought and documented for each participant choosing to participate in an approved project. Consent will be in lay terms and in a language understandable to the participant. (Preferably native language if the participant is not fluent in English.) Potential participants must be given sufficient time to have questions answered and to decide whether to participate. It must be explained that participation is voluntary and that choosing not to participate has no impact on benefits to which the participant is otherwise entitled. The consent process and document will contain the elements required in 45 CFR 46.116(a)(1-8) and 46.117 and 21 CFR 50.20, 50.25 and 50.27 as noted below and may contain additional elements in 45 CFR 46.116(b)(1-6), 21 CFR 50.25(b)(1-6) and institutional requirements, as applicable. Exculpatory language which releases or appears to release the institution, sponsor or investigator from liability or which makes or appears to make participants waive any legal rights cannot under any circumstance be included in the informed consent document or process.

Required basic elements of a consent document include:

- a statement that the study involves research,
- an explanation of the purposes of the research,
- an explaining of why the participant is being invited to participate,
- the expected duration of the participant's participation,
- a description of the procedures to be followed,

- identification of any procedures which are experimental,
- a description of any reasonably foreseeable risks or discomforts to the participant,
- a description of the safeguards to be used to protect participants from incurring the risk,
- a description of any benefits to the participant or to others which may reasonably be expected from the research,
- if applicable, a statement that participants will not benefit directly,
- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant,
- a statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained (for studies involving the use of drugs, devices or biologics, indicate that the FDA and sponsor may inspect records),
- a statement that the IRB and its staff may inspect study records,
- an explanation as to whether participants will be compensated for participation and if so the terms of the compensation,
- an explanation as to whether any compensation is available if injury occurs, and, if so, what it consists of, or where further information may be obtained,
- an explanation as to whether any medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained,
- an explanation of who to contact for answers to pertinent questions about the research and research participants' rights, and who to contact in the event of a research-related injury to the participants, and
- a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

Additional elements that the IRB may require within a consent document include:

- a statement that the particular treatment or procedure may involve risk to the participant which are currently unforeseeable (required when the study involves the use of investigational, drugs, devices or biologics, or drugs for which post marketing safety/efficacy data are being collected);
- a statement indicating the approximate number of participants involved in the study;
- a statement that the particular treatment or procedure may involve risks to the embryo or fetus, if the participant is or becomes pregnant which are currently unforeseeable (required when the study involves the use of investigational drugs, devices or biologics and participants are or may become pregnant or when there is insufficient data on how a marketed drug impacts embryos or fetuses and participants are or may become pregnant);
- anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent (required when the investigator may remove a participant from a trial due to medical /safety issues, participants inability to continue to provide informed consent, participant's noncompliance with the direction of the investigator, or other scenarios when the

investigator may determine it is in the best interest of the participant to withdraw them from the trial);
- any additional costs to the participant that may result from participation in the research (required if the participant will incur any permanent or temporary out-of-pocket expense related to participation in the trial, e.g., for procedures, drugs, research related injury, etc.);
- the consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant (required if the participant's decision to withdraw will raise safety concerns, e.g., withdrawal from medications that should be tapered rather than abrupt);
- a statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant (required for treatment trials or trials of moderate or more risk);
- disclosure of when a blind will be broken if the participant has an adverse event;
- disclosure of whether participants are / are not intended to share in financial gains resulting from the study (required when the study results may lead to the development of a product or technique that will provide financial benefit to HU, the sponsor, and/or the PI);
- a statement describing alternatives to course-required participation;
- an explanation that the study involves use of video or audiotaping, including a statement about how the recordings will be used and how long they will be kept. This statement should include who will see/hear the recording and where it will be used (e.g., in a classroom, professional meeting). If the investigator wants permission for the recording to be viewed/heard by anyone other than the research staff, or if it involves sensitive material, participants should also be given an opportunity to view (or listen to) the recording after it is completed. Permission for the tape to be used should then be obtained. The consent form must also clearly state who will transcribe the tapes and, if third-party transcriptionists will be used, what steps will be taken to protect participant confidentiality.

The IRB may require the following elements for studies involving genetic research:
- if family members may become aware of the information related to the study and to participant, or the participants may become aware of information about themselves or family members that they would preferred not to have known, that possibility must be disclosed by the PI in the consent form. Consent from the participant for disclosure of relevant information to relatives when the release of that information may improve the prognosis of the relatives will be sought. However, the participant must be made aware of the possibility of such a disclosure without consent. Disclosure that breaks confidentiality may occur if there is a treatment that will help the prognosis of the family member(s). To break confidentiality the following conditions outlined by the President's Commission (1983) must be satisfied:
    - reasonable efforts to obtain voluntary consent for disclosure have failed;
    - there is a high probability that harm will occur from withholding the information and that the disclosure will avert that harm; and

    - the harm that would likely occur would be serious.
    - only the information needed for diagnosis and treatment is disclosed;
- a statement that the action of the participants may place them risk (e.g., if they self disclose to their employer);
- a detailed description of what information will be presented to participants including:
    - what type of information will be provided to them or others,
    - who will provide the information,
    - how the information will be communicated,
    - at what point in the study it will be provided,
    - whether interim findings will be disclosed or not,
    - the reliability of the information being provided, and
    - what information will not be provided to them;
- if study information is intended to be shared with participants, the consent form must include an option whereby participants retain the choice of being told or not being told that information. An exception to the right not to know may occur when treatment could improve the prognosis. The PI must explain to the participant within the consent form whether the right not to know will be honored in such a circumstance;
- if the study is likely to yield unexpected or unrelated findings the consent must:
    - state that findings that do not affect the health of the participant or health of family members. For example, issues of maternity or paternity, will not to be disclosed,
    - either provide participants with an option of receiving or declining to receive information on unexpected and/or unrelated findings that are health-related, or
    - inform the participant that such information will be disclosed;
- information regarding genetic counseling by qualified genetic counselors if a study may reveal important genetic information, e.g., being a carrier for an illness that has not yet manifested. At whose expense the counseling is provided must also be disclosed.

B. Who May Obtain Consent

The PI or a qualified individual authorized by the PI on the IRB application may obtain informed consent. The individual who obtains consent must possess an in-depth knowledge of the protocol and be able to answer all questions posed by the participant. The individual obtaining consent must disclose their role in the study to the participant (e.g., PI, co-investigator, study coordinator, research assistant, etc.). The individual obtaining consent is required to have completed training in the protection of human participants in research. Completion of training will be verified through the screening of IRB applications and the auditing of approved studies.

C. Standard Consent and Documentation

With the few exceptions noted below, consent must be obtained from individuals of at least 18 years of age who are competent to give informed consent. Such individuals are considered to have decision-making capacity if (1) they have not been declared

incompetent by a court and (2) they are generally capable of understanding the consequences of alternatives, weighing the alternatives by the degree to which they promote their desire, and choosing and acting accordingly. The investigator is to make a practical assessment of the participant's capacity.

Consent will most often be documented using a long form consent document that satisfies the required elements of consent. The participant (or the participant's legally authorized representative) and the person obtaining consent must sign and date the form prior to study participation. The person obtaining consent must provide the participant (or the participant's legally authorized representative) with a copy of the signed and dated document. When it is feasible, the person obtaining consent must sign and date the form in the presence of the participant.

D. Waiver of Consent or Alterations to Elements of Consent

There are some scenarios by which it is possible for the IRB to waive or alter the elements of informed consent.

Scenario 1: The first method relates to studies that are conducted by or subject to the approval of state or local government officials (45 CFR 46.101(b)(5)). The study must also be designed to study, evaluate, or otherwise examine one or more of the following items:

i. public benefit of service programs;
ii. procedures for obtaining benefits or services under those programs;
iii. possible changes in or alternatives to those programs or procedures; or
iv. possible changes in methods or levels of payment for benefits or services under those programs.

The IRB must also find that the research could not practicably be carried out without the waiver or alteration. To request this method of waiver or alteration the investigator must complete the Waiver or Alteration of Consent section of the IRB-5 Exemption protocol application. The Chair will make the final determination as to whether or not to approve the request for an expedited study and IRB will make the determination for full board studies.

Scenario 2: PIs may request that the requirement of informed consent be waived or altered. In order to do so the investigator must complete the Waiver or Alteration of Consent section of the IRB-1 protocol application. The Chair will make the final determination as to whether or not to approve the request for an expedited study and the IRB will make the determination for full board studies. In order to do so the IRB must find that:

- the research involves no more than minimal risk to participants;
- the waiver or alteration will not adversely affect the rights and welfare of the participants;
- the research could not practicably be carried out without the alteration or waiver; and

- when appropriate participants will be provided with additional pertinent information regarding participation.

Alterations to the requirements of consent process allow for deviations from the regulatory requirements of consent but consent is still obtained. Examples of potentially approvable alterations to consent include:

- the use of implied/passive consent (e.g., via the return of completed surveys); or
- deception in research (see Informed Consent Requirements with Use of Deception in Research later in this document).

The IRB must find and document justification for any alteration to the requirements of consent. The request to waive or alter consent described in method 1 and 2 are not applicable to FDA regulated studies.

Occasionally investigators will seek information about individuals who are not principals to the research ("secondary participants"). These individuals could be members of the principal participant's family, sexual partners, friends, co-workers, etc. Such individuals may be participants in their own right, even if the investigator never has any contact with the individual. The federal regulations define a human participant not only as someone with whom the investigator interacts, but also as someone about whom the investigator seeks information. Therefore, the IRB must evaluate the consent process for each class of participant and will expect the protocol to describe an appropriate consent process for each such class. It may be possible for the investigator to ask the IRB to waive the requirement for consent, but only if the criteria described in scenario 2 are met.

E. Waivers of Documentation of Consent

In certain scenarios the IRB may still require that consent be obtained but waive the requirement to obtain documentation of consent. In order to do so the IRB must find that:

- the only record linking the participant to the study is the signed consent document and the principal risk would be harm resulting from a breach of confidentiality (participants must still be given the option of signing a consent document and the participant's wishes will prevail), or that
- the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

For studies subject to FDA regulations, only the latter provision is applicable.
If the requirement of documentation is waived, the IRB usually requires the investigator to provide the participant with a written summary of the research (i.e., "information sheet"). The IRB must review and approve that summary. The PI may request and the IRB may approve that a consent form also serve as the written summary.

F. Assessment of Participant’s Understanding of the Research and Consent Process

The IRB may require the PI or individual obtaining consent to confirm the potential participant's level of understanding, e.g., the IRB may require that the potential participant be able to describe in his/her own words the purpose of the study, the risks involved in the study, the possible benefits of the study either in writing or verbally with

or without a witness present. The PI can facilitate this process by asking the participant open-ended questions such as:

- Just so that I'm sure you understand what is expected of you, would you please explain to me what you think we're going to ask you to do?
- Describe in your own words the purpose of the study.
- What more would you like to know?
- What is the possible benefit to you of being in the study? What are the risks?

G. Consent from Emancipated Individuals

Emancipated individuals between the ages of 16 - 18 may provide consent to participate in research activities. The emancipated participant must provide proof of emancipated status. The person obtaining consent must attach this proof to the informed consent form. An emancipated individual does not meet the federal definition of child and therefore subpart D is not applicable.

H. Consent from Individuals Under 18 Years of Age for Certain Research Procedures

In specific circumstances, individuals under the age of 18 may provide consent to participate in research without demonstrating emancipated status when the research is limited to the categories noted below. In such circumstances the individuals are not considered children and therefore subpart D is not applicable.

1. All individuals under 18 years of age, if the research procedures are limited to:
    - HIV testing, counseling, and treatment
    - Outpatient mental health services
    - Testing or treatment for sexually transmitted diseases
    - Treatment or rehabilitation for alcohol or drug dependence
    - Abortion counseling and treatment
2. All individuals between 16 and 18 years of age, if the research procedures are limited to:
    - Inpatient mental health services
3. All individuals between 17 and 18 years of age, if the research procedures are limited to donation of blood or any component thereof and to the withdrawal of blood in conjunction with any voluntary blood donation program.

I. Informed Consent Requirements with Use of Deception in Research

The use of deception in research (e.g., participants are initially misinformed deliberately for purposes of the study) raises special issues that the IRB will review closely, especially with protected and vulnerable populations, including Native Americans. One consideration is whether the deception is necessary. An investigator proposing to use deception should justify its use. Federal regulations prohibit the use of deceptive techniques that place participants at greater than minimal risk. The IRB may modify the informed consent process for research involving deception when participants are not placed at risk. However, potential participants should be advised in the consent form that the information they are given is not complete and that they will be debriefed after the research procedures are completed.

The debriefing should include a detailed description of the ways in which deception was used. The investigator is responsible for ensuring that the participant leaves the research setting with an accurate understanding of the purpose of the research and why deception was used. The debriefing process, including any written materials, should be provided to the IRB as a part of submitted protocols. The following statement, or some similar statement, must appear in every consent form/information sheet for studies involving deception:
"Research designs often require that the full intent of the study not be explained prior to participation. Although we have described the general nature of the tasks that you will be asked to perform, the full intent of the study will not be explained to you until after the completion of the study. At that time, we will provide you with a full debriefing which will include an explanation of the hypothesis that was tested and other relevant background information pertaining to the study. You will also be given an opportunity to ask any questions you might have about the hypothesis and the procedures used in the study."

J. Consent by Phone/Fax

Consenting a participant, including consent from legally authorized representatives, is a process that should occur in person. Only for extenuating circumstances or minimal risk studies will the IRB consider the possibility of obtaining consent by phone or fax. The IRB may implement either of the following procedures:
Procedure 1:

- the potential participant must be given a copy of the approved, IRB-stamped consent document (either by mail, fax or e-mail of scanned document) prior to the phone conversation and with enough time allowed to read the document prior to the conversation;
- the individual obtaining consent must have a witness present for the entire conversation;
- participant must be informed that the witness is present and consent to the witness listening to the entire conversation (via speaker or extension phone);
- participant must be instructed that if s/he agrees to participate s/he must return the signed, dated and time stamped consent document (either by mail, fax or e-mail of scanned signed document); and
- the individual obtaining consent and the witness must sign, date and time stamp the IRB approved consent document upon completion of the phone conversation;

Procedure 2:

- the investigator requests a waiver of the requirement to document consent at the time of initial application or via a request for modification using the IRB-3 Amendment Review Form;
- a script of the phone conversation incorporating the elements of consent must be submitted to the IRB for approval;
- the IRB may require that the investigator provide participants with an IRB approved written statement (via mail, e-mail or fax) regarding the research.

In Procedure 1, the participant's signed and dated consent form must be received before any research intervention occurs.

K. Witnessing of Consent

The consent process generally does not have to be witnessed but the IRB may require this. For example, the IRB may require this when vulnerable or special classes of participants are involved in the study, the study is very complex in nature, or when the consent process occurs via phone. When an individual is signing the form as a witness, exactly what is being witnessed must be explained. For example, is the individual a witness to the signature only or a witness to the entire consent process? The IRB may determine what is required to be witnessed and who may serve as the witness. For example, the IRB may require that the entire consent process be witnessed by a research participant advocate, a representative of the IRB, research study personnel, a primary caregiver or other appropriate individual. Per Federal regulation 45 CFR 46.117(b)(2), a witness will be required if a short form written consent has been approved for oral presentation to the participant.

L. Requirement for Witness Signature on the Consent Form

It is possible to conduct an oral presentation of informed consent information in conjunction with providing 1) a short form written consent document stating that the elements of informed consent have been presented orally and 2) a written summary of what is presented orally. Per 45 CFR 46.117(b)(2), a witness must be present throughout the process. The IRB must approve the short form consent and a written summary of what is to be said to the participant or the representative (an approved informed consent form may serve as the written summary). At the time of consent the participant or the participant's representative signs and dates the short form. The witness shall sign and date both the short form and a copy of the summary, and the person actually obtaining consent shall sign and date a copy of the summary. A copy of the summary and the short form shall be given to the participant or the legally authorized representative. This process also applies to FDA regulated studies.

M. Consent for Participants Not Fluent in English

For participants not fluent in English, the consent process and document must be presented in a language (preferably native) understandable to them. Refer to the section on translation policy later in this document for more detailed information on the acceptable methods of translating documents. If it is expected that participants who do not speak English will be enrolled in a study, translated documents should be made available.

At times investigators may unexpectedly encounter a potential participant who does not speak/understand English. In such an event it may be acceptable to use the oral consent process. If using the alternative approach of an oral presentation of informed consent, as described above, a witness who is fluent in both languages must be present throughout the process. The English version of the informed consent form may serve as the summary form. The participant receives copies of the short form document and the summary. The oral presentation and short form document must be in a language (preferably native) understandable to the participant. At the time of consent the short form is signed and dated by the participant, the summary is signed and dated by the person obtaining consent, and both forms should be signed and dated by the witness.

The IRB must receive all foreign language versions of the short form document as a condition of approval under the provision of 45 CFR 46.117(b)(2). For studies initially reviewed via the full board, expedited review of the translated document is acceptable only if the English language version of the informed consent document and short form document have already been approved.

The IRB makes the final determination as to whether to require a complete written informed consent form or to accept an oral presentation of consent with the summary documents.

N. Consent Forms in Research Records

The PI will maintain the original informed consent document in a participant's research record or file. The participant must be informed of where the consent form (as well as other research related information) will be filed.

O. Re-Consenting Participants

The IRB requires that participants be re-consented if there have been developments that may affect a participant's willingness to continue to participate. The investigator must submit a request to amend the informed consent form to the IRB and then, after obtaining approval, re-consent the participants at the next regularly scheduled visit. Re-consenting a participant will serve to demonstrate that s/he has been informed of the additional information and that s/he willingly consents to continued participation. If the consent document has not yet been approved by the IRB at the time of the visit, a qualified member of the research team must provide a verbal explanation of the information to the participant and document the explanation in the research or medical record as appropriate to the study. In this circumstance, the participant is to sign the revised consent document at the next available opportunity.

The investigator or IRB may also determine that participants need to be contacted immediately depending on the nature of the information and the level of risk it presents to participants. This may occur prior to the consent document being approved. For example, if the PI learns that a drug is causing life threatening adverse events, the PI will determine the best way to communicate the information to the participants in the study. Consideration must be given to the participant's underlying condition, available support systems, and the nature of the information being conveyed. The PI must document the contact with the participants and inform the IRB of the contact.

Minor participants who are actively participating in a study when they reach the age of majority should be re-consented as adults at the next regularly scheduled visit.
If procedural changes are made to the informed consent form and those changes are not pertinent to an individual participant there is no need to re-consent. For example, if a procedure is added to the first visit and some participants have already progressed beyond that phase of the study they do not have to be re-consented. A member of the research team should however note in the record why the participant was not required to be re-consented.

If there are administrative changes to a consent document, e.g., in terms of contact names or numbers, participants still actively enrolled may be re-consented but it is not a requirement. However, the PI must ensure that the participants are provided with the revised information via letter, e-mail or some other means approved by the IRB.

P. Long-Term Follow-Up

Participants in long-term follow-up must be informed of outcome data and safety related information. They need not be informed of changes to the protocol if they are no longer in the active phase of the study. The PI will determine the mechanism of communication, giving consideration to the participant's underlying conditions, available support systems and the nature of the information being conveyed.

Q. Observation of Consent Process

The consent process may be observed by the IRB Monitor or other representative of the IRB. The observation will be done to ensure compliance with regulations and policy, for quality improvement and for educational purposes. Verbal consent of the participant may be sought prior to the observation.

R. Assent from Children or Decisionally Impaired Individuals

The IRB expects that children and those individuals who are not competent to provide consent should be given the opportunity to assent to participate in the research project. Assent is a knowledgeable agreement to participate in the project. Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively impaired persons who are capable of a knowledgeable agreement. In cases where assent is obtained from a child or cognitively impaired participant, permission must also be obtained from parents or legally authorized representatives. In accordance with the ethical principal of respect for persons, if the person from whom assent is sought refuses, the person should not be enrolled, even if the parents or legally authorized representatives give permission. Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parents or legally authorized representatives do not give permission. In rare circumstances, depending on the nature of the study and the age and circumstances of the child or decisionally impaired person, the IRB may waive the requirement for permission from parents or legally authorized representatives.

The scenarios outlined below are general and may be altered by the IRB depending on the nature of a specific study and the mental and physical status of the individual involved. The assent of the child may not be required in all situations. The IRB will determine, whether one or both parents must sign a parental permission form. The IRB may find that permission from one parent (or legally authorized representative) is sufficient for research involving no greater than minimal risk or for research involving greater than minimal risk but holding out the prospect of direct benefit to the participant. If the IRB finds that permission from one parent is sufficient the justification for this finding will be documented in the 'requires modification' and/or approval letters and, for full board reviews, in the minutes of a convened meeting.

If the participant is 12 years of age or older, the child signs and dates an assent signature line on the parental permission form and a parent or guardian also signs the parental permission form. In certain circumstances, the PI may propose or the IRB may require that a separate assent statement is necessary. For example, the PI may wish to reinforce the voluntary nature of participation and the nature of the study with minor participants in studies taking place at a school where the parents have already given permission of the minor participant to participate in the study.

If a separate assent form is required, both the form and the assent discussion with the participant should be in language especially tailored for the participant class and should describe the following:

- Explain why the study is being conducted;
- Describe what will happen and for how long or how often;
- State it is up to the child/individual to participate and that it is okay to say no;
- Explain if it will hurt and for how long and how often;
- Say what the child's/individual's other choices are;
- Describe any good things that might happen;
- Say whether there is any compensation for participating; and,
- Ask for questions.

The assent form should be limited to one page. Illustrations might be helpful and larger type makes it easier for some individuals to read. In studies involving older children or adolescents it may be possible for the child to read and indicate assent on the assent form. If the child is between 7-12 years of age, and the study is a therapeutic trial, the parent signs the parental permission form and the child participant does not have to sign. If the study is not a therapeutic trial, the parents or guardians sign the parental permission form and the participant signs an assent statement that is either included at the end of the parental permission form after the signature lines or as a separate document.

If the child is less than 7 years of age, the parent or guardian signs the parental permission form, the participant signs nothing. No assent statement is required. However, the PI or person obtaining consent must document in the study record that the child was willing to participate.

S. Consent from Illiterate Participants

At the onset of the consent process, the PI or designated individual authorized to obtain consent must ask the participant if any special provisions are required by them for the consent process, including having the consent document read to them. A witness to the process is required when obtaining consent from illiterate participants. An illiterate participant may make their mark on the consent form to indicate a willingness to participate. A video or audio tape of the process is recommended but the participant must consent to the taping and that consent must be on the tape. If taped, a copy of the tape must be provided to the participant and a copy must be retained with the study records.

T. Consent from Legally Authorized Representatives

When a potential participant is unable to provide consent due to impaired competency, it must be obtained from a legally authorized representative of the participant. Under DHHS and FDA regulations "legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the procedure(s) involved in the research. When research is conducted in Connecticut, the persons who meet the above definition are a child's parent(s), court-appointed conservators with specific authorization to consent to research, or court appointed guardians with specific authorization to consent to research, and individual who holds a research power of attorney.

Mentally retarded adults who have been declared incompetent must have an appointed legal guardian provide consent to participate in research. The natural parents of the adult are not authorized to give permission unless they have been appointed legal guardian(s). If a developmentally disabled adult has not been declared incompetent, the PI must decide if the participant is capable of understanding the elements of informed consent. A family member or other representative may be asked to co-sign. If the investigator determines the participant is not capable of providing consent, a legal guardian must be appointed and must provide consent before the participant can be enrolled.

U. Waiting Period Requirement
The IRB reserves the right to require a waiting period between the time a study is explained to a potential participant and/or the potential participant's representative, and the time consent is sought from the potential participant or representative. Scenarios when this option may be exercised include, but are not limited to, studies that involve vulnerable populations or studies that are of high risk.

V. Staged Consent Process
The IRB reserves the right to require a staged consent process whereby consent is obtained at various stages in the study to ensure the participant is still willing and/or still able to provide consent. Scenarios when this option may be exercised include, but are not limited to, studies that involve vulnerable populations, for example populations with diminishing capacity, longitudinal studies, or studies that are of high risk.

W. Considerations for Informed Consent for International Research
Field research done outside of the United States, especially in non-western societies or places where the participants do not speak English, poses some problems in obtaining written documentation of informed consent. In these situations, it is sometimes impossible, for a variety of reasons, to obtain written consent. If that is the case, the investigator must provide the IRB with a statement of the reasons why it should waive written consent, and also provide an acceptable alternative method of obtaining oral consent, which is appropriate to both the participants and their culture.

If the participants may be economically or educationally disadvantaged, the investigator should pay particular attention to these issues and ensure that appropriate safeguards have been implemented.

X. Informed Consent Requirements for Research with a Certificate of Confidentiality

A certificate of confidentially protects the participant's confidentiality by protecting research records from subpoena. The certificate goes beyond the consent form in ensuring confidentiality and anonymity. Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (usually as part of a criminal investigation of the participants). Certificates of Confidentiality are provided by the federal Department of Health and Human Services, however, the study's funding source is not relevant to the granting of a certificate.

While a Certificate of Confidentiality offers retroactive protection, it is advisable to apply for the certificate at least three months prior to the expected initiation of research procedures. It is helpful to the IRB for researchers to submit the certificate with their IRB application.

The following language is typical of Certificate of Confidentiality requirements. Either this or other similar language must be present in the consent form.
"To help protect your privacy, the researchers have obtained a Certificate of Confidentiality from the National Institutes of Health. With this certificate, the researchers cannot be forced to disclose the information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).
You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself and your involvement in the research. If an insurer, employer or other person obtains your written consent to receive research information, then the researcher may not use the Certificate to withhold that information.
The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant of the research project in instances such as evidence of child abuse or a participant's threatened violence to self or others."

Y. Recommendations for Translation of Documents and the Consent Process

Study related documents (e.g., the informed consent document, the HIPAA authorization, or survey instrument) must be presented in a language understandable to the participant. The IRB recommends the use of one of two methods for translation. One method is that the document be translated by a professional translation service that will attest to the accuracy of the translation. The second is the use of back-translation into English. In this scenario:

- the English version of the document is translated into the foreign language;

- the name and credentials of the individual who did the translation are provided to the IRB by the investigator;
- another individual who has not seen the English version of the document translates the foreign language document back into English;
- this individual provides his/her name, credentials and a statement that s/he has not seen the original English version to the IRB via the investigator;
- both English versions of the form and the foreign language version are submitted to the IRB for review; and
- the IRB will compare both English versions of the documents.

If the IRB determines that the translation is accurate, the foreign language document will be approved for use.

The informed consent process must also be conducted in a language understandable to the participant and may therefore require the use of a translator or sign language interpreter. In most cases, the translator may be a family member or friend of the participant, an employee of the institution or may be hired by the PI. The IRB will determine whether a professional translator is required on a case-by-case basis.
The PI is responsible for covering the cost of the translation. The cost of the translation will not be incurred by the participants.

If one of the two recommended methods is not feasible, the IRB will accept certification from the PI that he/she or a member of the research staff translated the document and that the translation is accurate. This verification must accompany submission of the translated documents.

Z. Health Insurance Portability and Accountability Act (HIPAA) and Research
The Health Insurance Portability and Accountability Act (HIPAA), also called the Federal Privacy Rule, went into effect on April 14, 2003. HIPAA requires that "covered entities" engaged in research maintain the privacy of the Protected Health Information (PHI) that is created, accessed or shared in the course of Research activity. A covered entity is a health care provider, payor, or clearinghouse that conducts certain types of electronic billing. PHI is individually identifiable information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions that can reasonably be used to identify an individual.

A request for the use and disclosure of PHI requires permission from each subject, called an Authorization to Use and Disclose Protected Health Information. "Use" of PHI is the sharing of PHI within the institution (i.e., from clinician to investigator). "Disclosure" of PHI is the sharing of PHI outside of the institution (i.e., from investigator to a participant's physician).

While the IRB is not responsible for HIPAA compliance at the covered entities on campus, the IRB will review each protocol on a case-by-case basis to ensure that when the HIPAA regulations apply, they are complied with. Each investigator is responsible for

complying with the HIPAA regulations from the institution(s) from which they wish to obtain PHI or where they will be conducting their research.

CHAPTER 5: VULNERABLE POPULATIONS

Studies proposing the involvement of vulnerable populations are reviewed to ensure that inclusion of these participants is justified and, if so, that adequate procedures are in place to minimize the risks related to physical harm, psychological harm and breach of privacy and confidentiality. The research must be relevant to the vulnerable population and not otherwise capable of being carried out with a non-vulnerable population. The IRB will fulfill the additional duties required by Federal Regulations outlined in Subparts B, C and D of 45 CFR 46 regardless of the source of funding for initial and continuing review by expedited or full board proceedings. For studies requiring full board review, a member or consultant who is knowledgeable about or experienced in working with vulnerable populations must review all material and be present (in person or via teleconference) at the meeting. The IRB Chair may use the IRB roster to identify such members and/or consultants to assign as reviewers. Consultants may participate in the discussion but may not vote. For studies requiring full board review, any decision made by a convened board will supersede the opinion of an individual reviewer. The minutes will reflect the determinations of the convened board regarding the required findings.

Vulnerable populations include those defined 45 CFR 46 Subparts B (Pregnant Women, Human Fetuses and Neonates), Subpart C (Prisoners), and Subpart D (Children), and those mentioned in 45 CFR 46.111(b): mentally disabled persons, or economically or educationally disadvantaged persons. The IRB also considers Heritage University students, employees, and HIV+ individuals to be vulnerable populations. The IRB may also require additional protections for any other group not specified in this policy but determined to be vulnerable by the IRB. Such additional protections may include, but are not limited to, the witnessing of the consent process, more frequent continuing review, or additional review by someone with a specific expertise.

I. Pregnant Women, Fetuses, or Neonates

Proposed studies involving pregnant women, fetuses or neonates may qualify for exempt or expedited review when no more than minimal risk is involved. The Chair or an IRB member will make the final determination. Studies requiring full board review will be reviewed and approved in accordance with the criteria of 45 CFR 46 Subparts A and B. The primary reviewers will be provided with the standard reviewer sheet that addresses Subpart A and information provided by the investigator that outlines the additional duties/findings required of the IRB under Subpart B. Unavailability of the father as related to consent issues is interpreted to mean that he is either deceased or that his whereabouts are not known and cannot be determined with a reasonable amount of effort. Note: The regulations specified in Subpart B apply when investigators engage in human participants research conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects unless the research is otherwise exempt from the requirements of the Common Rule or a department covered by a separate assurance. In cases where clinical research is not supported by the federal government, as described above, the University will apply equivalent standards when 45 CFR 46.204 applies. However, this may not always be possible in social/behavioral research because such research (while the risk is not greater than minimal risk) may not directly benefit the pregnant woman and/or the fetus. In order to engage in

social/behavioral research involving pregnant women, the IRB determined that it will allow pregnant women to be enrolled in research involving interview, focus group, survey or similar procedures. These studies will be reviewed by the IRB following equivalent standards as set forth in the Common Rule.

Pregnant women or fetuses may be involved in research only if the IRB finds that:

a) where scientifically appropriate, preclinical studies, including studies in pregnant animals, and clinical studies, including studies on pregnant women, have been conducted and provide data for assessing potential risks to pregnant woman and fetuses;
b) the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
c) any risk is the least possible for achieving the objective of the research;
d) the woman's consent is obtained in accordance with the provisions of Subpart A if the research holds out 1) the prospect of direct benefit to the pregnant woman, 2) the prospect of a direct benefit to both the pregnant woman and the fetus, or 3) no prospect of direct benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means;
e) if the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provision of Subpart A. The father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
f) each individual providing consent under paragraph d or e of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
g) for children who are pregnant, assent and permission are obtained in accord with the provisions of Subpart D – children involved as participants in research; (Subpart D is described under the section for children)
h) no inducement, monetary or otherwise, will be offered to terminate a pregnancy;
i) individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
j) individuals engaged in the research will have no part in determining the viability of neonates.

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

a) where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
b) each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

i. For neonates of uncertain viability, the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence or temporary incapacity, the legally effective informed consent of the either parent's legally authorized representative is obtained in accordance with Subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

ii. For nonviable neonates, the legally effective informed consent of both parents of the neonate is obtained in accord with Subpart A. The provisions to request a waiver or alteration of consent described in Subpart A do not apply. If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice. The consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice.

c) individuals engaged in the research will have no part in determining the viability of a neonate.
d) the following requirements have been met as applicable to neonates of uncertain viability.

i. until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the IRB determines that 1) the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and 2) any risk is the least possible for achieving that objective; or 1) the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and 2) there will be no added risk to the neonate resulting from the research;

ii. the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence or temporary incapacity, the legally effective informed consent of the either parent's legally authorized representative is obtained in accordance with Subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonates: After delivery a nonviable neonate may not be included in research unless all of the following additional conditions are met:

a) vital functions of the neonate will not be artificially maintained;
b) the research will not terminate the heartbeat or respiration of the neonate;
c) there will be no added risk to the neonate resulting from the research;

d) the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
e) the legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part. The provisions for a waiver or alteration of consent (46.116 c and d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice. The consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of the nonviable neonate will not suffice.

Viable neonates: A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D, Additional Protections for Children Involved as Participants in Research, describe in subsequent sections.

Research involving, after delivery, the placenta, the dead fetus, or fetal material may be conducted only if the IRB finds that:

a) research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State or local laws and regulations regarding such activities.
b) if information associated with material described in paragraph a of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research participants and must be afforded the applicable protections of 45 CFR 46 its subparts as applicable.

Research involving pregnant women, fetuses or neonates that does not fit into one of the above categories may only be conducted if the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problems affecting the health or welfare of pregnant women, fetuses or neonates and after the Secretary has consulted with an expert panel and there has been opportunity for public review and comment. The required findings for such research are that the research does present the aforementioned opportunity, the research will be conducted in accord with sound ethical principles and informed consent will be obtained.

II. Prisoners

The full IRB board must initially review all studies involving prisoners. The membership of the board will be such that the majority of members have no association with the prisons involved and at least one member will be a prisoner, or a prisoner representative. Such membership constitutes compliance with 45 CFR Subpart C 46.304, Composition of Institutional Review Boards where prisoners are involved. A prisoner representative will be assigned as the primary reviewer. The primary reviewer will be provided with the standard reviewer sheets that address Subpart A and information provided by the

investigator that outlines the additional duties/findings required of the IRB under Subpart C.

Minimal risk as related to studies proposing to involve prisoners is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examination of healthy persons. In assessing the level of risk involved in a study, the IRB will not use risks that face prisoners in the prison setting as the standard for acceptable risk, and will only allow risks that are commensurate with those that would be accepted by non-prisoner volunteers. The IRB must find that the involvement of prisoners as participants is justified.

Requests for amendments to approved studies that are administrative in nature and/or that pose no change to the involvement of the prisoner or to the level of risk, for example corrections of typographical errors in consent documents or additional data elements in a file review study, may be approved through the expedited review process by the Chair or the prisoner representative. However, the Chair or the prisoner representative reserves the right to require full board review of any request for modification.

Continuing review of studies involving prisoners will require full board review unless no participants have been enrolled and no additional risks have been identified or the remaining activity is limited to data analysis in which case the PI may request expedited review under category 8(b) or (c).
Per 46.305(a)(1), when reviewing proposals involving prisoners the IRB will ensure that the research is permissible under one of the categories of 46.306(a)(2) which are:

- study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- research on conditions particularly affecting prisoners as a class (e.g., vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice in the Federal Register of his intent to approve such research; or
- research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the participant. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice in the Federal Register of his intent to approve such research.

Per 46.305(a)(2-7), the IRB will also determine that the following additional criteria for approval have been satisfied:

- any possible advantages accruing to the prisoner through his or her participate in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the Board justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- the information is presented in a language which is understandable to the participant population; (note: use a 5th grade reading level as a benchmark)
- adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoner's sentences, and for informing participants of this fact.

When funding is from DHHS, the institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under Subpart C have been fulfilled. The certification letter will be sent from the RCC or IRB on behalf of the IRB.

III. Epidemiologic Research Involving Prisoners

Effective June 20, 2003, the Secretary of the DHHS may also approve epidemiologic research involving prisoners as participants under a provision allowing for a waiver of the applicability of provisions 46.305(a)(1) and 46.306(a)(2) as set forth above. While prisoners may be included in such studies, they cannot be the only population included within the study. The epidemiologic research can present no more than minimal risk and no more than inconvenience to the prisoner-participants. To qualify for such a waiver the epidemiologic study must meet the following criteria:

- the sole purposes are to describe the prevalence or incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease, and
- for DHHS supported research, the IRB, via the RCC or IRB, must include in the certification letter to OHRP that the additional criteria of 46.305(a)(207), as described above, have been satisfied.

- that the research presents no more than minimal risk and no more than inconvenience to the prisoner-participants, and
- prisoners are not a particular focus of the research

Studies for which the waiver may apply include epidemiological research related to chronic disease, injuries, and environmental health.

IV. Children

Research that involves children is subject to the additional requirements of Subpart D. Under DHHS and FDA regulations "children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

When research is conducted in Washington, persons who meet the above definition are all individuals under 18 years of age with the following exceptions:

1. Individuals between 16 and 18 years of age adjudicated as emancipated by a probate court
2. All individuals under 18 years of age, if the research procedures are limited to:
    a. HIV testing, counseling, and treatment
    b. Outpatient mental health services
    c. Testing or treatment for sexually transmitted diseases
    d. Treatment or rehabilitation for alcohol or drug dependence
    e. Abortion counseling and treatment
3. All individuals between 16 and 18 years of age, if the research procedures are limited to:
    a. Inpatient mental health services
4. All individuals between 17 and 18 years of age, if the research procedures are limited to donation of blood or any component thereof and to the withdrawal of blood in conjunction with any voluntary blood donation program.

Proposed studies involving children may qualify for exempt or expedited review if the study falls into one of the federally-approved categories defined in 45 CFR 46.101 or in the guidance published in the Federal Register for categories for which expedited review is acceptable. Exemption categories 1-5 do not apply to FDA regulated studies. Also the exemption noted at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research involving children unless the research involves the observation of public behavior and the investigator(s) do not participate in the activities being observed. The Chair will make the final determination regarding approval status and categories. Studies requiring full board or expedited review will be reviewed and approved in accordance with the regulatory criteria as summarized below. The primary reviewers will be provided with the standard reviewer worksheets that address Subpart A and information provided by the investigator within the protocol that outlines the additional duties/findings required of the IRB under Subpart D.

For research not involving greater than minimal risk, the IRB must find and document that adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

For research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants the IRB must find and document:

- the risk is justified by the anticipated benefit to the participants;
- the relation of the anticipated benefit to the risk is at least as favorable to the participant as that presented by available alternative approaches; and
- that adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

For research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition the IRB must find and document:

- the risk represents a minor increase over minimal risk;
- the intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- the intervention or procedure is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for the understanding or amelioration of the participant's disorder or condition; and
- that adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

For research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children the IRB must find and document:

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and
- for studies funded by DHHS, the Secretary, after consultations with a panel of experts in pertinent disciplines and following opportunity for public review and comment, has determined either that the research in fact satisfies one of the set of conditions described above, or the following:
- the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles; and
- adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

For studies regulated by the FDA, the Commissioner of Food and Drugs, after consultations with a panel of experts in pertinent disciplines and following opportunity for public review and comment, has determined either that the research in fact satisfies one of the set of conditions described above, or the following:

- the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles; and
- adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

The IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. The judgment may be made for all children to be involved in research under a particular protocol, or for each child. When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Assent is not a necessary condition for proceeding with the research if the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. The IRB may also waive the assent requirement under provisions noted in 45 CFR 46.116 and/or 21 CFR 50.55(d)(1-4). Examples when assent might be waived include certain school-based behavioral studies or studies that meet the criteria under 45 CFR 46.101(b)(1).

In accordance with and to the extent that consent is required under regulation, the IRB shall determine that adequate provisions are in place for soliciting the permission of each child's parents or guardian. Under DHHS regulations, "guardian" means an individual who is authorized under applicable State or local law, to consent on behalf of a child to general medical care. Under FDA regulations "guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research, or an individual who is authorized to consent on behalf of a child to participate in research.

When research is conducted in Washington, the persons who meet the definition of guardian are court-appointed guardians with the authority to consent to major medical, psychiatric or surgical treatment with specific authorization to consent to research. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research not involving greater than minimal risk or research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants. If the research is greater than minimal risk and offers no prospect of direct benefit to individual participants, but is likely to yield to generalizable knowledge about the participant's disorder or condition or is not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent

or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

In addition to the provisions for waiver of consent contained in DHHS regulations, if the IRB determines that a research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participant (e.g., neglected or abused children) it may waive the consent requirements in 45 CFR 46 provided an appropriate mechanism for protecting the children who will participate as participants in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity status and condition. This is not applicable to FDA regulated studies. Permission by parents or guardians shall be documented in accordance with and to the extent required by regulations. FDA regulated studies do not qualify for the exception to the requirement to document consent noted at 46.117(c)(1).

Per regulations, children who are wards of the state or other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to the individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition, or research that is not approvable under a defined regulatory category but that presents an opportunity to understand , prevent , or alleviate a serious problem affecting the health or welfare of children only if the research is 1) related to their status as wards, 2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards. If the research is approved, the IRB will require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may be the advocate for more than one child. The individual acting as the advocate shall have the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except as the advocate or IRB member) with the research, the investigators, or the guardian organization.

V. Economically or Educationally Disadvantaged

Economically or educationally disadvantaged individuals may be particularly vulnerable to the risks of research. The IRB may require additional protections. For example, the IRB may require the use of a witness to the consent process or videotaping the consent process.

Educationally disadvantaged participants may not be able to fully understand the concepts presented by the research and the investigator must take extra precautions to ensure that the participants fully understand what is being asked of them.
Similarly, economically disadvantaged participants may be easily persuaded to participate in research if the economic compensation is so great that it would result in the participant ignoring or disregarding the research risks because of the income offered by the study. In such cases investigators must be careful to set economic compensation at a

meaningful level that compensates the participant for her/his time, but it not so great that it unduly influences a participant's decision to enroll. It is also important in such cases that the risks to the participants be made clear to the participants.

VI. Heritage University Students

Studies that focus on Heritage University students as participants may raise concerns with issues of coercion, undue influence and privacy. While these studies may qualify for exempt or expedited review, the Chair, or authorized designee reserves the right to require full board review. The IRB may consult with students when considering approval of a study that involves them as participants.

Each application that involves students as participants must outline procedures to ensure that the students will not be subject to undue influence or coercion and to ensure that the student's privacy will be respected. While a PI may use his/her own students as participants, it is preferable for the PI to recruit students with whom he/she does not have a direct relationship. If it is not possible or practical to recruit from the general population of students due to the nature of the research (e.g., research on teaching methods or curriculum development) the study must be designed in such a way that any element of undue influence or coercion is minimized.

Suggestions to minimize elements of undue influence and coercion include anonymous data collection methods and the use of an independent third party to collect data or consent participants (a graduate teaching assistant in the class in which the student/participant is enrolled does not qualify as a third party for collecting the data on behalf of the instructor). In this way, the instructor does not know who did or did not participate. Another is to hold off seeking consent until after course grades have been determined. For example, if the research project involves evaluating the effectiveness of a new teaching method, once final grades are determined, consent from the student should be sought as to whether his/her individual information can be used in the research study. In this way, the element of coercion is minimized since grades would already have been determined. Students should also be recruited by a general announcement, central posting or announcement mechanism and should include a clearly written description of the project and a statement of the proposed student participation. In addition to being provided with the traditional information and consent forms, the student should also be provided with the name and contact information of a neutral third party to contact should they feel coerced at any time during the process. Note: The PI is required to submit the proposed study to the IRB prior to implementing the new teaching method that is the subject of the research and at that time may request the IRB's approval to delay the consent process. Also, the IRB suggests that when students are the targeted population, any payment for participation should be proportionate to the expense incurred with participation, for example parking expenses. Because students are often under financial constraints, larger payments may influence decisions to enroll.

As with all participants, participation must be voluntary and based on disclosure of complete and accurate information. Students should not be asked to participate in any study that will interfere with their curricular activities and obligations. A student's

decision to participate or not participate can not have any bearing on grades awarded by the instructor.

If extra credit is awarded for participation in a study, other comparable means of earning the same amount of extra credit must be available to those students who choose not to participate. Examples of other comparable means include: short papers, special projects, book reports, and brief quizzes on additional readings, research seminars, or completing a similar project. These projects should be comparable in terms of time, effort and educational benefit to participation as a research participant to ensure that students are not being pressured or coerced into becoming participants.

Whenever possible, researchers should avoid data collection during regular class meetings. When study participation consumes a significant portion of a class section, loss of instructional time for both participants and non-participants may be considered a loss of benefits. Also, when research participation is expected during the same session at which participation is invited, students may be unduly influenced to take part due to peer pressure, perceived stigmatization from non-participation, or a sense of having otherwise wasted time by attending that day's class.

Since there are special risks of confidentiality in the close environment of the university, special attention should be given to full disclosure of these risks in the consenting of a student to participate. The plan for handling research data should also be designed to minimize the risk that confidentiality will be breached. When instruments call for the disclosure of information which participants may view as personal or sensitive, data should be collected in a manner that minimizes the chance of one participant learning the response of another.

Students must be allowed to withdraw from the study at any time. The informed consent statement should make clear the consequences of withdrawing from a project prior to completion. In general, it is favorable to give credit if the participant withdraws, unless the student withdraws immediately or there is evidence of bad faith on the part of the student.

If the research is such that data are collected from a group project or perhaps a videotape of the group interaction, each student's consent is necessary for the use of that data in the instructor's research. If one student does not consent, the data may be used only if the non-consenting student's data can be effectively excluded.

Students have the right to full disclosure as soon as possible. Whenever possible a teaching opportunity in the form of an "educational debriefing" should be employed. Students should know something about the rationale for the study, the process of data collection, and intent of the researcher. In exceptional circumstances, the full or true purpose of the research may not be revealed to the participants until the completion of data collection. In such cases, students must not be subjected to undue stress or embarrassment and must have the right to full disclosure of the purpose of the study as soon as possible after the data have been collected. During the debrief students should be

told why the use of deception was necessary to carry out the research and be given an opportunity to decide whether the researcher(s) can use the data collected (refer to Informed Consent Requirements with Use of Deception in Research).

Research conducted by graduate students in a class in which the researcher teaches, assists in the class, or does any grading will be subject to the same restraints described above.

VII. Heritage University Employees

Studies that focus on Heritage University employees as participants may raise concerns of coercion, undue influence and privacy. While these studies may qualify for exempt or expedited review, the Chair or authorized designee reserves the right to require full board review. The IRB may consult with employees when considering approval of a study that involves them as participants.

Within each application that involves employees as participants, the PI must outline procedures to ensure that the employees will not be subject to undue influence or coercion and to ensure that the employee's privacy will be respected. While a PI/supervisor may use his/her own direct report employees as participants, the preference of the IRB is that the PI recruit employees with whom the PI does not have a direct relationship. For example, if the research study is an analysis of the performance evaluation process, the PI may recruit employees from the general population of the institution as opposed to employees from the PI's department. If colleagues or subordinates will be recruited the PI must provide a rationale for their recruitment other than for convenience sake.

Additional suggestions to minimize concerns of coercion, undue influence and privacy include the general recruitment of participants through IRB approved advertisements, collection of data in an anonymous method, the use of an independent third party to recruit, consent and/or collect data. The IRB will also closely review how study data is reported back to management.

The employee's participation must be voluntary and based on disclosure of complete and accurate information. Employees should not be asked to participate in any study that will interfere with their job obligations. An employee's decision to participate or not participate can not have any bearing on the employee's performance evaluation.
The IRB will follow these same policies and procedures when it reviews research studies that seek to enroll non-Heritage University employees in research.

VIII. Decisionally Impaired

Individuals considered to be decisionally impaired may include those with psychiatric, cognitive or developmental disorders, substance abuse problems or individuals in chronic pain. Studies involving decisionally impaired participants may qualify for exempt or expedited review. However, the Chair or designee reserves the right to require full board review. Individuals who are decisionally impaired may still be capable of providing consent. If evidence is present that they are incapable of providing informed consent, for

example, due to the incapacity to understand, an individual who is legally authorized to consent for them must sign and date the consent document. The IRB will make a determination as to whether the target participant population is capable of providing consent or whether a legally authorized representative must provide consent. The IRB may also require additional protections such as a witness to the consent process or requiring the PI to determine on an individual basis whether an individual is capable of providing consent, e.g., the IRB may require that the PI ask the participant to articulate in his/her own words the purpose of the study, the risks involved with the study, the benefits of the study and may request that those responses be documented. If the participant cannot answer such questions, consent from a legally authorized representative must be obtained.

When reviewing protocols that focus on decisionally impaired participants as the target population, the IRB must find that they are an appropriate participant population for the study, that the research question focuses on an issue unique to this population, that the level of risk is appropriate to the study and that, unless a waiver or alteration of consent has been approved, the provisions for obtaining informed consent from a legally authorized representative and the assent of the participant are adequate.

The IRB will use the additional protections set forth in Subpart D 46.404 (Research not involving greater than minimal risk), 46.405 (Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants), 46.406 (Research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition) or 46.407 (Research not otherwise approvable via 404, 405 or 406 which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of the individuals) as guiding standards for the review process. Legally authorized representative will be substituted for reference to parent or guardian made in subpart D. Research involving decisionally impaired adults that would fall under category 407 will not require a Secretarial consult but the IRB may call upon consultants with additional expertise.

The provisions for obtaining the assent of an individual with impaired decision making ability are based on those set forth in subpart D. The IRB shall determine that adequate provisions are made for soliciting the assent of the decisionally impaired individual, when in the judgment of the IRB the individuals are capable of providing assent. In determining whether the individuals are capable of assenting, the IRB shall take into account the maturity and psychological state of the individual involved. This judgment may be made for all individuals to be involved in research under a particular protocol, or for each individual, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the individuals is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the individual and is available only in the context of the research, the assent of the individual is not a necessary condition for proceeding with the research. Even where the IRB determines that the participants are capable of assenting, the IRB may still waive the assent

requirement under circumstances in which consent may be waived in accord with 46.116(d)(1-4). For FDA regulated studies, assent may be waived in accordance with 50.55(d)(1-4).

The IRB may impose additional protections. For example, the IRB may require the use of a witness to the consent process or videotaping the consent process. The IRB may also require that the investigator consider the following issues and address each issue as appropriate:

The investigator should explain how he/she plans to determine competency to consent. Observed deficits in cognitive or mental status testing may indicate need to evaluate participant's decision making in more detail. Cognitive functions related to competency are attention, abstraction, judgment, reasoning, memory, learning, comprehension, language expression, mood and affect. In addition, severe decisional impairment to the extent that institutionalization (nursing home, hospitalization) is probable or actual for the potential participant should be considered a criterion in the determination of competency to consent. Components of the research consent capacity should be evaluated and documented during the consent process. The investigator should address how he/she will separate the roles of clinician and clinical investigator, if applicable.

It should be recognized that decision-making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing and periodic reconsent may be needed. The investigator should describe his/her process for reconsent or reassent or reassessment of willingness to continue participation.
As impairment increases, along with risks and discomforts, safeguards should increase according to a sliding scale, i.e., protections should be proportional to the severity of capacity impairment, or to the magnitude of experimental risk, or both.

IX. HIV-Infected Individuals

HIV-infected individuals will be considered a vulnerable population because of the risks of social stigma, employability and insurability facing them if their HIV status were revealed. The University will comply with federal and state guidelines, including those concerning notification of seropositivity, counseling, and safeguarding confidentiality where research activities directly or indirectly involve the study of human immunodeficiency virus (HIV).

All research with HIV-infected individuals is reviewed by the full IRB to ensure that the participants' rights and privacy are thoroughly safeguarded. At such a review the IRB may determine that a particular research study is sufficiently low in risk so as to allow continuing review to be conducted on an expedited basis. Research about HIV/AIDS that does not include HIV-infected individuals may be considered exempt or expeditable.
In addition, the IRB will consider the guidelines set forth from OHRP with regards to AIDS/HIV Related Research (OHRP: Institutional Review Board Guidelines, Chapter 5, Section F). When necessary the IRB may call upon consultants with additional expertise in this area.

X. Members of the Armed Forces

Studies that focus on military personnel may also raise concerns of coercion, privacy and, in particular, undue influence. While these studies may qualify for exempt or expedited review, the Chair or authorized designee reserves the right to require full board review. The IRB may consult with military personnel when considering approval of a study that involves them as subjects.

Within each application that involves military personnel as participants, the PI must outline procedures to ensure that personnel will not be subject to undue influence or coercion and to ensure that the employee's privacy will be respected. The IRB suggests that PIs review the Department of Defense (DoD) directive 3216.2 (Reissued March 25, 2002). While this directive concerns clinical research studies, it describes additional protections for certain categories of research that go beyond those outlined in 32 CFR 219 (the DoD implementation of the "Common Rule" Federal Policy) and are relevant for social and behavioral research. The directive includes the following requirements (see section 4.3) to minimize concerns of coercion, undue influence and privacy as they apply to more than minimal risk studies. The requirements include ensuring that unit officers and noncommissioned officers (NCOs) shall not influence the decisions of their subordinates to participate or not to participate as research participants. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate. These requirements should also be taken into consideration for studies not supported by the DoD. The IRB will also closely review how study data is reported back to officers.

The service member's participation must be voluntary and based on disclosure of complete and accurate information. Military personnel should not be asked to participate in any study that will interfere with their responsibilities. A service member's decision to participate or not participate can not have any bearing on the service member's performance evaluation.

XI. Non-English Speaking Individuals

The involvement of non-English speaking individuals in research studies raise concerns with issues of informed consent as well as their inclusion and exclusion in research. While these studies may qualify for exempt or expedited review, the Chair or authorized designee reserves the right to require full board review.

Investigators must be aware that individual participants, and sometimes significant portions of the potential participant population, may not speak English. Investigators

must plan for populations that are likely to be recruited into the research and incorporate translations into the study design to allow for appropriate recruitment and enrollment. When applicable, the PI must outline in the protocol application procedures to recruit non-English speaking participants as well as procedures to translate study material and consent documents. The protocol must also describe procedures for ensuring that informed consent is presented to participants in a language understandable to them. Procedural requirements for the informed consent process for these participants can be found in the informed consent section of the policies (see Consent for Participants Not Fluent in English).

Non-English speaking participants, who meet enrollment criteria, may not be excluded because they cannot understand or read English. Non-English speaking participants may not be excluded from research that may have direct potential benefits. If non-English speaking participants will be specifically excluded from research, the PI must provide an ethical and scientific explanation for doing so.

XII. Indigenous Populations

Indigenous knowledge, traditional resources, and properties are central to the maintenance of identity for indigenous peoples. Traditional resources include plants, animals, and other material objects that may have sacred, ceremonial, heritage, or aesthetic qualities. Property for indigenous peoples has intangible, spiritual manifestations. The term Traditional Resource Rights (TRR) is used to define the many 'bundles of rights' that can be used for protection, compensation, and conservation of resources and properties of indigenous peoples. TRR includes basic human rights, the right to self-determination, collective rights, land and territorial rights, intellectual property rights, rights to protection of cultural property, folklore and cultural heritage, the recognition of cultural landscapes, and recognition of customary law and practice. Every indigenous community has its own customs and laws covering privacy, respect, permission, and compensation for its people during research, exploitation or non-indigenous uses of traditional resources or properties.

Heritage University recognizes and respects TRR of indigenous peoples and undertakes to inform faculty, staff, and students that these must be considered before any activity is undertaken involving TRR. University personnel working with indigenous peoples are expected to adhere to Section III.A. of the Code of Ethics of the American Anthropological Association. If requested by Heritage University, the principal or lead investigator must be prepared to certify that advance permission has been obtained from appropriate individuals or groups of the indigenous peoples to be studied and that the research procedures comply with all applicable tribal, state, and federal laws.

Among American Indian/Alaska Native (AI/AN) nations, groups have rights in addition to those held by individuals. Among those rights are protection of traditional ways of thinking and connecting to the land, the plants, the animals, and the rocks of the places where indigenous people live. Indigenous people have the right to protect their knowledge, their language, their traditional resources, their ceremonies, their songs, and

their traditional properties. As sovereign nations, they have the right to regulate what happens on their lands.

It is the intent of this IRB to be responsive to the concerns and needs of the Yakama Nation. If a researcher intends to conduct research about tribal culture, traditions, language, physical or emotional health, or about the current practices on a tribal reservation, it is the responsibility of the researcher to contact the indigenous nation, find out what their protocol for approving research is, follow that protocol, and obtain permission for the study to proceed. The IRB will ascertain if that process has been followed.

A research proposal for American Indian/Alaska Native people should pay particularly careful attention to confidentiality. Indigenous communities may be small and tightly-knit making confidentiality both more important and more difficult to maintain than in other studies. Protocols should describe precautions for safeguarding the confidentiality of participants. Further, because indigenous people are fewer in number than other populations, they are more easily identifiable. The research protocol should describe how identifiers will be coded or removed.

Some indigenous communities remember being humiliated by research or deceived by it. If deception is necessary, then the research proposal should explain the need for it and describe why the benefit to the community outweighs the risk of damage because of humiliation or deception.

An IRB-1 proposal for American Indian/Alaska Native people should be conducted with the purpose of supporting the interests and visions of the research participants as they define them.

CHAPTER 6: IRB APPLICATION & REVIEW PROCEDURES

I. Human Subjects Research Training

All investigators, co-investigators, and lead personnel are required to complete human subjects research training and certification before submission of any IRB applications for review. Collaborative Institutional Training Initiative (CITI) provides HU with online training and certification for faculty, staff, students, and other personnel involved in human subjects research. Review of IRB proposals will take place only after CITI certification of all investigators, co-investigators, and lead personnel is completed.

II. Advance Submission

IRB applications (research proposals) are to be submitted to the IRB Office for review at least 30 days before the planned start-up date for the research. No definitive action such as recruiting participants, expending funds, or submitting a grant proposal to an outside agency may proceed before written approval for the research is obtained.

III. Content of Research Proposal.

Proposals submitted for review shall be contain the following: a) a rationale explaining the nature, purpose, and potential benefits of the research**;** b) a description of the research methods, with particular emphasis on procedures that pose a risk to participants, involve deception, or do not maintain the participant's anonymity to all parties beyond investigative personnel; c) description of the potential participant pool and the means of recruitment**;** and d) copies of any written recruitment materials and consent forms, or of information given retroactively to participants.

The following forms will be used to cover the above criteria:

- IRB-1: Full IRB and Expedited Review
- IRB-1A (completed with IRB-1): Drug Device
- IRB-1B (completed with IRB-1): Genetic
- IRB-1C (completed with IRB-1): Treatment
- IRB-2: Reapproval/Completion of Study
- IRB-3: Amendment Review
- IRB-4: Adverse/Unanticipated Events
- IRB-5: Request for Exempt Review
- IRB-6: Protocol Deviation Form
- IRB-7: Research Methods Courses (RMC)
- IRB-8: Reapproval/Completion of RMC/IRB-7
- IRB-9: Ethnographic/Naturalistic Research

IV. Review and Approval of Proposals

All research proposals are first submitted to the IRB office. The IRB Administrator reviews the proposals for completeness, clarity, and eligibility for exempt or non-exempt status. He/she then forwards the proposals to the chairperson of the IRB with either conditional approval as exempt or a recommendation for either expedited or full board review.

A. Requests for Exempt Status

Investigators seeking "exempt" status for research should prepare an IRB-5 form, using the standard application form on the IRB website. The proposal should clearly explain why the research is believed to be low risk and should qualify for exempt status.
The IRB Chair will review the proposal. The IRB chairperson will review the submitted proposal and either approve the exempt status for the research, or designate the proposal for expedited review or full board review. He/she will forward one copy of the proposal (with his/her decision regarding the review status) to the Provost office and will retain the other copy of the proposal for the IRB Office files.

When the IRB-5 is received in the Provost office, the IRB administrative staff will notify the investigator of the outcome of the review. If the study has been approved with exempt status, a "Certification for Exemption" will be sent to the investigator. The research may proceed when the investigator receives the exempt certification. If the IRB chairperson does not approve the exempt status for the research, the investigator will be advised of procedures to obtain the required review.

Research studies approved for exempt status are not routinely monitored by the IRB while the study is in progress. However, the investigator (or supervising faculty member in the case of student research) is responsible for informing the IRB Office of the completion date of the approved research study.

Instructors of research methods courses (RMC) that educate students on designing and executing research should consult the IRB Administrator and/or IRB Chair regarding the projects their students will be working on in their classes. RMC instructors with projects that operate in controlled facilities (i.e. public schools), work with protected/vulnerable populations, or other human subjects activity as deemed by the IRB Administrator and/or IRB Chair may need to submit an IRB-7 form to the IRB Office. Instructors seeking RMC reapproval or concluding their courses should complete an IRB-8 form.

B. Expedited Review:
From the viewpoint of the investigator, the procedures for expedited review are the same as those for full board review. An IRB-1, IRB-7, or IRB-9 (ethnographic/naturalistic research) application form is completed and submitted with the research proposal and supporting documents. The proposal shall contain a complete description of the proposed research or study, including provisions for the adequate protection of the rights and welfare of prospective human research participants and assurance that the pertinent laws and regulations are observed. Samples of study materials, communications with prospective participants and any informed consent forms shall be included.

For studies meeting the eligibility criteria for expedited review, two copies of the research proposal are submitted to the IRB chairperson. The proposal is read by the IRB Administrator and/or IRB Chair who takes one of two actions: (i) referral of the proposal to the full board for review, or (ii) referral to an IRB member (including the Chair) for expedited review. Note: Reviewers doing expedited reviews cannot disapprove research proposals.

In the case of stipulations, the approval is conditional, and the investigator must respond to the stipulations in a communication with the IRB Chair. Upon receipt of a satisfactory response to the stipulation(s), the IRB Chair will then give approval. In the case of recommendations, the investigator may proceed without further communication from the IRB. If the IRB Chair judges the proposal to require full board review, the proposal shall be relayed to the full board and the investigator notified in writing to that effect.

C. Full Board Review:
If the unit designate recommends full board review of a submitted proposal, ten copies of the IRB-1, IRB-7, or IRB-9 are to be forwarded to the IRB Administrator and/or IRB Chair. When the application is received, it will first be screened for completeness. If information is missing from the application, the investigator will be contacted and requested to supply the missing information. Applications are assigned to one of the monthly Board meetings for review on a "first come, first served" basis. A week or more before the scheduled meeting, applications are posted on the confidential IRB website for review by board members.

Upon review, the Board shall make one of three determinations:

1. **Approval**
2. **Modifications Needed:** The Board will explain in writing why the proposal, as submitted, needs modification. The investigator may not take any definitive action such as recruiting participants, expending funds, or submitting a grant proposal to any outside agency that requires institutional review board certification until a proposal, with modifications is approved by the IRB.
3. **Disapproval:** If a proposal is not approved, the IRB will in explain, in writing, the rationale for the disapproval and notice of the appeal options under this policy. Without approval the investigator shall not use any university facilities or funds for the research, nor in any way claim university sponsorship. The university will not incur any obligation to protect an investigator who proceeds with the research nevertheless.

V. Approval Timeframes:
Research activities are approved for no longer than a period of one year and may be approved for a shorter period of time commensurate with the level of risk posed by the research and the projected project duration. [45 CFR 46.109]. The approval letter sent to the investigator will specify the time period that research activities may be conducted. No research data may be collected outside of the designated time period. Research projects that cannot be completed in the approved time period will need a continuation approval via an approved IRB-2 form.

When reviewing the initial proposal, the following criteria will be used by the IRB to determine the frequency of study review: 1) the probability or magnitude of anticipated risks to participants, 2) any medical conditions of the proposed participants and their susceptibility to problems as a result of enrollment in the protocol, 3) qualifications of the investigator and other members of the research team, 4) past history of the investigator(s) and research team in adherence to IRB guidelines, 5) specific experience of the

investigator(s) in similar research protocols, 6) the nature and frequency of adverse events in similar research, 7) the general vulnerability of the population being studied, and 8) other factors deemed relevant to the IRB.

VI. Applications for Continuation of Previously Approved Studies

The IRB shall be informed at least annually of the status of all research. As a courtesy to investigators, administrative staff assigned to IRB support functions will send a notice and IRB-2 or IRB-8 form to the investigator one month before the end of a given approval period. An investigator who does not receive such a reminder should contact the IRB Office as soon as possible to request a copy of the Status Report. If the research is proceeding in relation to participants as outlined in the research protocol, the investigator is to note this on the IRB-2 or IRB-8 form. If there are any significantly increased risks to participants, deceptive practices in the research, or if any other changes have occurred (or are expected to occur) that could affect the rights and choices of participants, the investigator shall not wait until the annual status report but shall promptly submit updated information to that effect to the board for its review.

VII. Study Modifications.

It is recognized that changes to a research study and informed consent documents may be required as the research proceeds. However, proposed modifications must be approved by the IRB before they are implemented. The only exception to this requirement is a procedural change that may be necessary to eliminate an apparent immediate hazard to a research participant. If this occurs, the investigator must submit an IRB-3 amendment form or IRB-6 protocol deviation form with the original proposal to make it consistent with the changes. If a research study is completed prior to the end of the approval period, the investigator should submit an IRB-2 form to the IRB Office, noting the date of study closure.

VIII. Appeal Process

If an investigator believes that the IRB review process was not fairly executed and that it resulted in an unduly restrictive decision regarding the proposed research, he/she may appeal the decision. He/she should first discuss the matter with the IRB chairperson, taking care to explain the reasons for believing that the research procedures are in compliance with University policy and federal and state regulations. If the issue cannot be resolved satisfactorily by negotiation, the investigator may appeal the decision of the reviewer(s), in writing, to the Authorized Institutional Official, and then the Provost.

Upon receipt of an appeal the AIO or Provost shall convene an ad hoc committee, constituted so as to fulfill federal requirements, and with the majority of members being past but not current members of the IRB. The ad hoc committee will consider the appeal, and within 60 days, communicate its decision in writing to the Provost, giving its reasoning for the decision. A copy of the decision will be given to the investigator and the current IRB chairperson, and documented in the minutes of the next convened IRB meeting.

Any person who proceeds with collecting or analyzing research data, intentionally disregarding the need for official approval of the IRB for the research, will be in violation of IRB policy and will be subject to administrative sanctions, including the termination of research privileges at the University.

CHAPTER 7: MONITORING THE CONDUCT OF RESEARCH

I. Oversight Responsibilities

Protection of human participants in research is a shared responsibility of many persons in the academic community, including those directly engaged in the conduct of the research (e.g., investigators and study personnel), those with specific review and oversight responsibilities (IRB and AIO), University administrative officers, and the wider academic community.

All persons engaged in the conduct of research are expected to be aware of HU policies regarding human subjects research and are obligated to report observed violations to the IRB. The IRB provides ongoing education on human participant[s] research for the University community through new faculty orientation sessions, online education/training modules, and individual consultations as requested. Members of the IRB and all investigators are required to complete CITI certification training approved by the IRB. Persons engaged in research support roles are also required to complete CITI certification training.

A. Investigator Responsibilities and Reporting Requirements

The primary responsibility for the day-to-day protection and welfare of research subjects lies with the investigator who submitted the IRB application. This person is expected to implement the study in a safe and timely manner, according to the approved proposal, and to keep the IRB informed of any unanticipated problems or adverse events. During the course of the study, and up to three years after completion of a study, he/she must keep detailed records of all research-related activities, (e.g., lists of enrollments, copies of consent and assent forms, minutes of meetings, lists of meetings and attendees), and make the records available for IRB review upon request.

In the case of student research, the student and supervising faculty member share responsibility for monitoring the safety of human participants, and are held accountable for these activities.

B. Unexpected Events and Adverse Reactions

During the course of a research study, unexpected events and adverse reactions may occur to a study participant, other individuals associated with the participant, or to key personnel associated with the research study. An unexpected event is an unanticipated problem associated with any aspect of the research study that may involve risks to the enrolled study participants and/or to other individuals who may or may not be directly associated with the research study. This type of event can happen in both clinical and non-clinical (behavioral or social science) studies. An adverse reaction is an undesirable and unintended, though not necessarily unexpected, result of therapy, study interventions or activities. These generally occur in clinical research and only apply to participants enrolled in the study. Investigators are responsible for ongoing monitoring of their studies for unexpected events and adverse reactions, and reporting these situations to the IRB if they arise using the IRB-4 form.

II. IRB Monitoring of Approved Studies

The IRB tracks all research studies. It also has procedures for systematic monitoring of all non-exempt studies while they are being conducted. If it finds any human subject concerns or violations (or if these are reported to the IRB), it will make every attempt to work collaboratively with the principal investigator to ensure that corrective actions are taken.

A. Routine Monitoring

The following IRB procedures are used for routine monitoring of approved studies:

1. Review of investigators' credentials and IRB training certifications: Primary Investigators must show evidence of having completed the IRB-approved human participant research training before start-up of a research project. A copy of the CITI training certificate can be attached to the IRB application or sent to the Provost office.
2. Computerized tracking of research studies, with documentation of IRB application approval dates, annual reviews, and notations of any protocol changes or reported human subject concerns;
3. Annual (and other required) Status Reports (IRB-2; IRB-8);
4. Administrative staff assigned to support IRB functions routinely monitor non-exempt research studies in the tracking system for timely submission of Status Reports and any other required documentations from investigators. An alert will be sent to any investigator having a delinquent Status Report, reminding him/her that the approved study period has lapsed and the study may not proceed. If there is no acknowledgement within 10 days, direct contact will be made with the investigator to determine whether the research study has been completed. In the event that the study is still in progress (without the required Status Report), it is in violation of IRB policy, and the investigator will be instructed to desist from all project activities. The violation will also be recorded in the IRB minutes.

Student research projects associated with coursework and must have IRB approval via IRB-7 (if needed) for one or two semesters. The supervising faculty member is responsible for ensuring that the IRB is kept informed of the status of the student project. If the approved project period has lapsed without notification of project completion, the faculty member will be contacted and asked to submit the required status report IRB-8.

1. Random Audits

Random samples of non-exempt studies in progress may be selected for periodic audits. When this occurs, a designated person from the IRB meets with the investigators of the audited studies to discuss the progress of the studies and review the study records. A report is generated for the IRB and feedback is given to the investigators.

2. Unexpected Events/Adverse Reactions

If a report of an unexpected event or adverse reaction is filed with the IRB (IRB-4), an investigation is held to determine the seriousness of the situation and its potential effect on the safety of study participants and other persons (risk/benefit analysis). If the safety concerns can be adequately addressed by modifications of study procedures, the

investigator will be asked to make the modifications and submit an amendment to the original proposal (IRB-3), verifying his/her intent. If risks to the research participants or other persons cannot be adequately addressed by procedural modifications, the research study will be suspended or terminated.

3. Follow-up on reported human subject concerns and/or violations
Any telephone calls or other verbal or written communications that come to the attention of the AIO, IRB Office, or Provost's office concerning human participant matters in individual studies will be forwarded to the IRB chairperson for follow-up. An investigation of the concern or allegation will be initiated within 10 working days.

B. Additional Monitoring and Verification of Safety and Compliance
There may be situations in which the IRB determines that it needs to do additional monitoring, and/or collect information from sources other than the investigator to verify that no material changes have occurred in the study since previous IRB review or that no other human subject violations have occurred. Situations that may require additional monitoring and/or verification include: a) studies that involve unusual levels or types of risks or that include vulnerable groups as research participants, b) a study conducted by an investigator who has previously failed to comply with IRB or federal regulations, or c) concerns raised about changes occurring in a study, based on information in submitted Status Reports, or d) human participant concerns reported to IRB members or the Provost office.

Various sources may alert the IRB of the need for an independent review of an ongoing study. Inquiries may be submitted from: committees or administrative units within the University; community agencies collaborating on a project; enrolled research participants or family members; the news media; a funding agency; the Office of Research Protections (OHRP) or other federal or state agencies.

In these cases, the IRB will determine whether: 1) an audit of the research study needs to be conducted by the Provost's office, 2) the research should be suspended, and/or 3) if additional administrative actions need to be taken. If an investigation is required, a designated person from the IRB will meet with the investigator to discuss the reported concerns/violations (without revealing the identity of the person(s) initiating the report). He/she is authorized to review any study documentations, interview study staff and/or study participants, or directly observe the research proceedings to obtain information needed for an impartial assessment of the situation. Needed corrective actions will be discussed with the investigator, and a written report will be given to the IRB and Provost. Additional follow-up visits or contacts may be initiated by the IRB to verify that corrective actions have been taken. Oversight of assigned senior researchers and/or IRB members can be used to ensure that no more violations occur.

C. Federally-Funded Clinical Trials.
Federally-funded research studies that include activities classified as Phase I or Phase II clinical trial research by the National Institutes of Health (NIH) or other federal funding agencies are required to have a "Data and Safety Monitoring Plan" in place to document

safeguards for research participants. The IRB follows and endorses federal policy with regards to the need for additional monitoring for such intervention studies. If an investigator intends to submit a protocol that entails clinical trials research, a preliminary Data and Safety Monitoring Plan should be submitted with the IRB application. The IRB will consult with the investigator on development of the Data Safety and Monitoring Plan or provide advise on external resources. Investigators planning to participate in multi-center collaborative research are encouraged to seek guidance from established clinical trials networks and the DHHS Office of Research Protections (OHRP). This should be done in addition to completing the required IRB-approved human participant research training.

D. Suspension or Termination of Research

The IRB has the authority to suspend or terminate at any time its approval of research that is not being conducted with the IRB's requirements or that has been associated with unexpected serious harm to subjects [45 CFR 46.113]. Any suspension or termination shall be conveyed promptly to the principal investigator, with reasons for the board action conveyed in writing.

E. IRB Reporting Requirements

The DHHS regulations [45 CFR 46.103(a) and (b) (5)] require that institutions have written procedures to ensure that the following incidents related to nonexempt research conducted under an OHRP-approved assurance are promptly reported to the OHRP:

- any unanticipated problems involving risks to subjects or others;
- any serious or continuing noncompliance with federal policy or requirements or determinations of the IRB;
- any suspension or termination of IRB approval.

Any of the above problems will be promptly reported to appropriate institutional officials, and to the DHHS Office of Research Protections (OHRP) when applicable. Incident reports submitted to the OHRB will include the following information: a) name of the University (HU); b) full title of the research study; c) name of the primary investigator (person currently responsible for conduct of the research); d) number of the study assigned by the IRB (and any number of any applicable federal award, e) a detailed description of the problem, and f) actions the University is taking or plans to take to address the problem.

The Provost or his/her appointed representatives are responsible for communications with the OHRP and/or other governmental or regulatory agencies for compliance purposes. The IRB will cooperate with any compliance investigations initiated by the University or the OHRP.

CHAPTER 8: IRB DOCUMENTATIONS

I. Maintenance of Research Records

A. The university shall maintain adequate documentation of IRB activities, including the following:

- Copies of all research proposals submitted for notification or review.
- Copies of all progress reports, changes in research as related to the rights of participants, and reports of injuries to participants.
- Minutes of IRB meetings, in sufficient detail to show attendance, board actions, the vote on these actions in terms of the number of members voting for, against, or abstaining, the basis for requiring changes in a proposal or disapproving it, and a brief summary of the discussion of controversial issues and their resolution.
- Records of continuing notification and review activities and copies of all correspondence between the board, its unit designates, and investigators.
- The written policies and procedures of the board.

B. For each non-exempt study approved by the IRB, the retained records shall include:

- the research proposal and supporting documents;
- copies of all correspondence between the IRB and investigators; including copies of all progress reports, changes in research as related to the rights of participants, and reports of injuries to participants.
- adverse event reports of injuries to participants or unapproved changes in study procedures;
- records of initial and continuing review and any amendments to the proposal and/or consent forms;
- progress reports submitted by investigators and statements of significant new findings provided to study participants.

C. Studies granted exempt status by the IRB are not subject to ongoing IRB monitoring and record retention so long as there is not a change in the proposed aims or procedures. However, the dates of the project start-up and completion of exempt studies are recorded in the IRB tracking system.

II. Timeframes for Record Retention

All IRB records required by this policy shall be retained for at least three years. Records related to research that is conducted shall be retained for at least three years after completion of research, and will be accessible for inspection and copying by authorized representatives of the OHRP and other federal agencies.

Investigators conducting exempt studies are advised to retain study forms and documentation of research activities for three years or as required by the academic administrative unit, and they are responsible for notifying the IRB of the date of completion of the study.

CHAPTER 9: IRB MEMBERSHIP & MANAGEMENT

I. Board Member Appointments & Responsibilities.

A. The IRB consists of at least five members appointed by the University President.

- At least three members of the IRB shall be faculty.
- One member shall not be otherwise affiliated with the university and shall not be a part of the immediate family of someone who is affiliated with the university.
- Members shall include at least one whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

B. Members of the IRB are appointed by the president for three-year overlapping terms. The Provost, deans, and other faculty information sources may be consulted in order to identify appropriately qualified members to serve on the board.

C. Members shall not vote on proposals in which they have a conflict of interest. The board may invite individuals with special competencies to assist with proposal review. These individuals will not vote.

II. Liability

Heritage University will defend and indemnify the IRB members, the IRB Administrator, IRB Chair, and AIO for claims that arise from their good faith performance of IRB duties.

III. Physical Resources and Administrative Support

The IRB operates out of the Provost office, where physical space is available for storage of confidential materials and convening of board meetings. The IRB also has access to other conference rooms on campus that are adequate for proposal presentations and discussions.

The Provost office provides administrative staff support for IRB functions. Typical support tasks include activities such as facilitating communications between the IRB and investigators regarding the submission and disposition of research proposals, maintaining confidential research files, managing the computerized tracking system (including entry of new studies, status report notifications, reports for IRB review), and managing IRB correspondence. Additional support for compliance oversight is provided via internal faculty/staff assignments or by external consultation contracts as the need arises.

Financial resources are available thru the Provost office to support any required human participants research training for the IRB and investigators. Additional funding is

available for institutional memberships in organizations that support human participant research standards, and for the IRB chairperson or other designated Board members to purchase needed education materials or attend national and regional conferences on human participant research.

CHAPTER 10: DEFINITIONS

ANONYMOUS: Subjects' identities are unknown to the investigator, not requested, and not given. If the only time the investigator asks for a name is for a signature on a consent form, the investigator should use implied consent, to preserve anonymity.

APPLICATION: The formal design or plan of a study's activity; specifically, the plan submitted to an IRB for review and to an agency for support. The application includes a description of the design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen (s), and the proposed methods of analysis that will be performed on the collected data.

ASSENT: Agreement by subjects not competent to give legally valid informed consent (e.g., children or cognitively impaired people) to participate in a study. Refers to a child's affirmative agreement to participate in the research. Mere failure to object should not, absent affirmative agreement, be construed as assent. "Children" are persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. § 46.402 *From Informed Consent A Guide to the Risks and Benefits of Volunteering for Clinical Trials* (Kenneth Getz & Deborah Borfitz, 2002): p. 130, "Children aren't expected to give their consent, but they're often asked to give their assent." "IRBs consider parental permission sufficient if the research is going to be done on young children (vaguely defined as somewhere under the age of seven to 11) who lack the intellectual and emotional ability to understand what they're agreeing to."

ASSURANCE: A formal written, binding commitment that is submitted to a federal agency, in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved.

BELMONT REPORT: A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1979.

BENEFIT: A valued or desired outcome to the study that will be an advantage to the subjects participating. Compensation is not considered a benefit.

BIOMEDICAL RESEARCH: Studies that are designed to evaluate the safety, effectiveness, or usefulness of an intervention include research on therapies (*e.g.*, drugs, diet, exercise, surgical interventions, or medical devices), diagnostic procedures (*e.g.*, CAT scans or prenatal diagnosis through amniocentesis, chorionic villi testing, and fetoscopy), and preventive measures (*e.g.*, vaccines, diet, or fluoridated toothpaste). It can also include normal human functioning and development, compare the functioning of a particular physiological system at different stages of development (*e.g.*, infancy, childhood, adolescence, adulthood, or old age), or define normal childhood development. It includes records research used to develop and refine hypotheses. Research on specific

disease (*e.g.*, research on the biochemical changes associated with AIDS or schizophrenia, or the neurological changes associated with senile dementia of the Alzheimer type) and the human genome and genetic markers fall under biomedical research. Biomedical research is focused on:

1. specific diseases and health conditions (mental or physical), including: detection, cause, treatment, prevention, and rehabilitation;
2. evaluation and testing of the safety, effectiveness, or usefulness of an intervention, treatment, or therapy;
3. normal and abnormal physiology, human functioning, and development;
4. cognitive, emotional, and behavioral responses to real or potential health problems;
5. the human genome and genetic markers;
6. the incidence and prevalence of illness and injury among populations, and strategies for prevention and health promotion.

CERTIFICATE OF CONFIDENTIALITY**:** A Certificate of Confidentiality helps researchers protect the privacy of human research participants enrolled in biomedical, behavioral, clinical and other forms of sensitive research. Certificates protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a research participant. Any research research that collects personally identifiable, sensitive information and that has been approved by an IRB is eligible for a Certificate. Federal funding is not a prerequisite for Certificate. For more information: http://grants.nih.gov/grants/policy/coc/index.htm.

CERTIFICATION: Official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

COMMON RULE: A large majority of Federal Agencies simultaneously published a regulation or "Common Rule" on June 18, 1991 to regulate the conduct or support of human subject research. The rule is set forth in 45 CFR Part 46, Subpart A. Subpart A consists of 45 CFR 46.101 to 46.124.

CONFIDENTIAL: Subjects' names are known to the investigator and are usually coded to a master list and/or kept separately from the data and results. This is usually used, for example, when the investigator must match test results with surveys or if there will be a follow-up survey. The investigator must have a need to know subjects' names.

CONTINUING REVIEW: Approved research will undergo review until the completion or termination of the research, including scheduled continual reviews of research that will occur at least annually.

CRIME: A crime is a wrongdoing which has been classified by the state or federal legislative body as a felony or misdemeanor.

DATA: Refers to information that is collected for analysis or used to reason or make a decision.

DECEPTION: Deception is the intentional misleading of subjects or the withholding of full information about the nature of the experiment. Misleading or omitted information might include the purpose of the research, the role of the researcher, or what procedures in the study are actually experimental. Deception increases ethical concerns, because it interferes with the ability of the subject to give informed consent. However, deception is arguably necessary for certain types of behavioral research. Because humans act differently depending on circumstances, full knowledge by the subject might bias the results.

DIRECTLY OR INDIRECTLY IDENTIFIABLE: Identities of individual subjects are kept by the investigator. If subjects' identities are inseparable from data, then data is ***directly*** identifiable. If subjects' identities are kept separate from data, with information connecting them maintained by codes and a master list, then data is ***indirectly*** identifiable. In either case, the investigator must assure that confidentiality will be maintained, and must explain how subjects' identities will be protected.

- *Direct identifiers:* Direct identifiers in research data or records include names; postal address information (other than town or city, state and zip code); telephone numbers, fax numbers, e-mail addresses; social security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate /license numbers; vehicle identifiers and serial numbers, including license plant numbers; device identifiers and serial numbers; web universal resource locators (URLs); internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; and full face photographic images and any comparable images.
- *Identifiable data or records:* contains information that reveals or can likely associate with the identity of the person or persons to whom the data or records pertain. Research data or records with direct identifiers removed, but which retain indirect identifiers, are still considered identifiable.
- *In-direct identifiers:* Indirect identifiers in research data or records include all geographic identifiers smaller than a state , including street address, city, county, precinct, Zip code, and their equivalent postal codes, except for the initial three digits of a ZIP code; all elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such age and elements may be aggregated into a single category of age 90 or older.

EDUCATIONAL SETTING: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management method.

EXEMPT: The Common Rule specifies that research activities may be classified as exempt in the policy if human subjects involvement is limited to one of the listed scenarios, including studies involving the collection or study of existing data when those data either are publicly available or are not personally identifiable. Exempt determinations are evaluated by IRB staff and will take approximately 10 working days for certification once they arrive at the IRB Office.

GENERALIZABLE KNOWLEDGE: Knowledge that could be applied to populations outside of the population served by the covered entity. This definition can vary. Examples of activities that typically are not generalizable include:

- biographies
- oral histories that are designed solely to create a record of specific historical events
- service or course evaluations, unless they can be generalized to other individuals
- services, or concepts where it is not the intention to share the results beyond HU or any agency supporting the research
- classroom exercises solely to fulfill course requirements or to train students in the use of particular methods or devices
- quality assurance activities designed to continuously improve the quality or performance of a department or program where it is not the intention to share the results beyond the HU community

HIPAA: Health Insurance Portability and Accountability Act (HIPAA) of 1996 that protects certain health information. The Privacy Rule was issued to protect the privacy of health information that identifies individuals who are living or deceased.

HUMAN SUBJECT: A living individual about whom an investigator (whether professional or student) conducting research obtains a) data through intervention or interaction with the individual, or b) identifiable private information.

INFORMED CONSENT: The knowing, legally effective consent of any individual or the individual's legally authorized representative; such consent can be obtained only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

INTERPRETER/ TRANSLATER: An agent of the researcher(s), whom assists in the facilitation of communication between the researcher(s) and participants who are not fluent in the language of the researcher(s).

INSTITUTIONAL REVIEW BOARD (IRB): A committee formed to facilitate the protection of human subjects in research.

INTENTIONALLY IDENTIFIED: Subjects' names are identified in connection with the data when the research results are presented to the public. This procedure is common for journalistic-type interview studies, where subjects are public figures or in oral histories.

In these cases, the investigator should seek explicit consent from the subjects for the use of their names in connection with their data.

INTERACTION: Includes communication or interpersonal contact between investigator and subject.

INTERVENTION: Includes both physical procedures by which data is gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

IRB APPROVAL: The determination by the IRB that the research has been reviewed and may be conducted within the constraints set forth by the IRB and other institutional and federal requirements.

MINIMAL RISK: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed study is 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. The definition of minimal risk for research involving prisoners differ somewhat from that given for non-institutionalized adults.

NEONATE: Newborn (viable or non-viable).

NON-EXEMPT**:** The Common Rule specifies that research activities may be eligible for expedited review if the protocol involves only minimal risk or a previously reviewed protocol is receiving modifications that are only minor. Non-exempt review is carried out by three IRB Members. Such expedited reviews have the force of full reviews, except that if the protocol is found not acceptable, then it must receive review by the full committee; the Chair or designee alone cannot reject a proposal. Expedited reviews are reviewed as the packets are received and will take approximately 12 working days for review once they have arrived at the IRB Office. Full board applications are reviewed at the next scheduled IRB meeting.

ORAL HISTORY: Tape-recorded historical information obtained in interviews concerning personal experiences and recollections. Often, the intention is that these tapes become available to the public at a specified future time in order to convey historical insight.

PERSONALLY IDENTIFIABLE HEALTH INFORMATION: Health or medical data or information that can be linked manifestly or inferentially to an individual.

POPULATION: A group of people in society meeting certain criteria to be eligible as subjects in a research’s protocol.

PRINCIPAL INVESTIGATOR (PI): The individual with primary responsibility for the design and conduct of a research study.

PRISONER: A prisoner is defined by federal regulations as any individual involuntarily confined or detained in a penal institution and/or individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to incarceration.

PRIVACY: Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

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 which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

PROTECTED HEALTH INFORMATION: Individually identifiable Health information recorded in any form or medium that is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse and relates to the past, present, or future physical or mental health or condition of an individual, the provision of health care to an individual, or the past, present, or future payment for the provision of health care to an individual.

PUBLICLY AVAILABLE DATA: Public sources of data, such as census data.

RESEARCH: Systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of the IRB, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. Research:

- includes all theses, dissertations, publications, and/or presentations;
- designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships);
- generally does not include operational activities such as practice activities in medicine, psychology, social work, and public health (e.g., routine outbreak investigations and disease monitoring) and studies for internal management purposes such as program evaluation, quality assurance, quality improvement, fiscal or program audits, marketing studies, or contracted-for services;
- generally does not include journalism or political polls.
- However, some of the above activities may include or constitute research in circumstances where there is a clear intent to contribute to generalizable knowledge.

RISK: The probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a study. Both the probability and magnitude of possible harm may vary from minimal to significant.

SIGNIFICANT RISK: A study's design that presents a potential for serious risk to the health, safety or welfare of the subjects.

SUBSTANCE ABUSE: Substance abuse refers to the use of substances when said use is causing detriment to the individual's physical health or causes the user legal, social, financial or other problems, up to, and including, endangering their lives or the lives of others. Substance abuse is not specific to illegal substances. Substance abuse also includes the abuse of legal substances which are legitimately purchased or prescribed.

SYSTEMATIC: Step-by-step, methodical procedure presented or formulated as a coherent body of ideas or principles.

VOLUNTARY: Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (and/or to continue to participate) in a research activity.

APPENDIX A: The Belmont Report

(Taken from http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html)

1. Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

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2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

3. Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

*** *David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

*** *Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*

*** *Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

*** *Deceased.*

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4. Table of Contents

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5. Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes (1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical

problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

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6. Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

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7. Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then

dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

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8. Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an

adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus

requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought,

and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

APPENDIX B: DHHS Code of Federal Regulations [45 CFR 46]

(Taken from http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html)

Code of Federal Regulations

TITLE 45
PUBLIC WELFARE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised January 15, 2009
Effective July 14, 2009

* * *

Subpart A-- Basic HHS Policy for Protection of Human Research Subjects

Sec.

Subpart B -- Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Sec.

Subpart C -- Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Sec.

Subpart D -- Additional Protections for Children Involved as Subjects in Research

Sec.

Subpart E -- Registration of Institutional Review Boards

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

Editorial Note: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost--sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

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Subpart A	Basic HHS Policy for Protection of Human Research Subjects
	Authority: 5 U.S.C. 301; 42 U.S.C. 289(a); 42 U.S.C. 300v-1(b).
	Source: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102, must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
(i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(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 and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution

afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.[1]

[1] Institutions with HHS-approved assurances on file will abide by provisions of Title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or
(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, 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* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort 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.

(j) *Certification* means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§46.103 Assuring compliance with this policy -- research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101(b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with §46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Human Research Protections, HHS, or any successor office.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §46.101(b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§§46.104--46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB

§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §46.103(b)(4) and, to the extent required by, §46.103(b)(5).

(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, 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 list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

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 non-expedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate 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 suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101(b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other

eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B	Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
	Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions.

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§46.205 Research involving neonates.

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

(3) Individuals engaged in the research will have no part in determining the viability of a neonate.

(4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Subpart C	Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
	Source: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *DHHS* means the Department of Health and Human Services.

(c) *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8366, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(ii) Study of prisons as institutional structures or of prisoners asincarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D	Additional Protections for Children Involved as Subjects in Research
	Source: 48 FR 9818, March 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of subpart A are applicable to this subpart.

[48 FR 9818, Mar.8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991.]

§46.402 Definitions.

The definitions in §46.102 of subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) *Parent* means a child's biological or adoptive parent.

(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the

assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Subpart E	Registration of Institutional Review Boards
	Source: 74 FR 2399, January 15, 2009, unless otherwise noted.

§46.501 What IRBs must be registered?

Each IRB that is designated by an institution under an assurance of compliance approved for federalwide use by the Office for Human Research Protections (OHRP) under §46.103(a) and that reviews research involving human subjects conducted or supported by the Department of Health and Human Services (HHS) must be registered with HHS. An individual authorized to act on behalf of the institution or organization operating the IRB must submit the registration information.

§46.502 What information must be provided when registering an IRB?

The following information must be provided to HHS when registering an IRB:

(a) The name, mailing address, and street address (if different from the mailing address) of the institution or organization operating the IRB(s); and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer or head official of that institution or organization who is responsible for overseeing activities performed by the IRB.

(b) The name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.

(c) The name, if any, assigned to the IRB by the institution or organization, and the IRB's mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address.

(d) The name, phone number, and electronic mail address of the IRB chairperson.

(e)(1) The approximate numbers of:

(i) All active protocols; and

(ii) Active protocols conducted or supported by HHS.

(2) For purpose of this regulation, an ``active protocol'' is any protocol for which the IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure during the preceding twelve months.

(f) The approximate number of full-time equivalent positions devoted to the IRB's administrative activities.

§46.503 When must an IRB be registered?

An IRB must be registered before it can be designated under an assurance approved for federalwide use by OHRP under §46.103(a).

IRB registration becomes effective when reviewed and accepted by OHRP.

The registration will be effective for 3 years.

§46.504 How must an IRB be registered?

Each IRB must be registered electronically through http://ohrp.cit.nih.gov/efile unless an institution or organization lacks the ability to register its IRB(s) electronically. If an institution or organization lacks the ability to register an IRB electronically, it must send its IRB registration information in writing to OHRP.

§46.505 When must IRB registration information be renewed or updated?

(a) Each IRB must renew its registration every 3 years.

(b) The registration information for an IRB must be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information or the IRB chairperson. The updated registration information must be submitted in accordance with §46.504.

(c) Any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period.

(d) An institution's or organization's decision to disband a registered IRB which it is operating also must be reported to OHRP in writing within 30 days after permanent cessation of the IRB's review of HHS-conducted or -supported research.

APPENDIX C: Federal Drug Administration (FDA) Regulations [21 CFR 50]

(Taken from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=50) and http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1)

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 50 PROTECTION OF HUMAN SUBJECTS

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.
Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2012]
[CITE: 21CFR50]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 50 PROTECTION OF HUMAN SUBJECTS

Subpart A--General Provisions

Sec. 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999; 66 FR 20597, Apr. 24, 2001]

Sec. 50.3 Definitions.

As used in this part:

(a)*Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040*et seq.* as amended (21 U.S.C. 321-392)).

(b)*Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or

repealing a standard for these products, described in part 809.

(15) An *Application for an Investigational Device Exemption,* described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.

(23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, or for a health claim, described in 101.70 of this chapter.

(25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.

(c)*Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the

Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d)*Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e)*Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f)*Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g)*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h)*Institution* means any public or private entity or agency (including Federal, State, and other agencies). The word*facility* as used in section 520(g) of the act is deemed to be synonymous with the term*institution* for purposes of this part.

(i)*Institutional review board* (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase*institutional review committee* as used in section 520(g) of the act.

(j)*Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(k)*Minimal risk* means that the probability and magnitude of harm or discomfort 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.

(l)*Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's particpation in the procedure(s) involved in the research.

(m)*Family member* means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

(n)*Assent* means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

(o)*Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

(p)*Parent* means a child's biological or adoptive parent.

(q)*Ward* means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

(r)*Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in 50.25.

(s)*Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51528, Oct. 2, 1996; 62 FR 39440, July 23, 1997; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 66 FR 20597, Apr. 24, 2001]

Subpart B--Informed Consent of Human Subjects

Sec. 50.20 General requirements for informed consent.

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations

unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

[46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

Sec. 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the

use of the test article.

(d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has

reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to

be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

(e)(1) Obtaining informed consent for investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents will be deemed feasible unless, before use of the test article, both the investigator (e.g., clinical laboratory director or other responsible individual) and a physician who is not otherwise participating in the clinical investigation make the determinations and later certify in writing all of the following:

(i) The human subject is confronted by a life-threatening situation necessitating the use of the investigational in vitro diagnostic device to identify a chemical, biological, radiological, or nuclear agent that would suggest a terrorism event or other public health emergency.

(ii) Informed consent cannot be obtained from the subject because:

(A) There was no reasonable way for the person directing that the specimen be collected to know, at the time the specimen was collected, that there would be a need to use the investigational in vitro diagnostic device on that subject's specimen; and

(B) Time is not sufficient to obtain consent from the subject without risking the life of the subject.

(iii) Time is not sufficient to obtain consent from the subject's legally authorized representative.

(iv) There is no cleared or approved available alternative method of diagnosis, to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.

(2) If use of the investigational device is, in the opinion of the investigator (e.g., clinical laboratory director or other responsible person), required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (e)(1) of this section in advance of using the investigational device, the determinations of the investigator shall be made and, within 5 working days after the use of the device, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(3) The investigator must submit the written certification of the determinations made by the investigator and an independent physician required in paragraph (e)(1) or (e)(2) of this section to the IRB and

FDA within 5 working days after the use of the device.

(4) An investigator must disclose the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in the report to the subject's health care provider and in any report to public health authorities. The investigator must provide the IRB with the information required in 50.25 (except for the information described in 50.25(a)(8)) and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and public health authorities.

(5) The IRB is responsible for ensuring the adequacy of the information required in section 50.25 (except for the information described in 50.25(a)(8)) and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.

(6) No State or political subdivision of a State may establish or continue in effect any law, rule, regulation or other requirement that informed consent be obtained before an investigational in vitro diagnostic device may be used to identify chemical, biological, radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that is different from, or in addition to, the requirements of this regulation.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999; 71 FR 32833, June 7, 2006; 76 FR 36993, June 24, 2011]

Sec. 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a

result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects

will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section

and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

Sec. 50.25 Elements of informed consent.

(a)*Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of

treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b)*Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for

inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on*http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

(d) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(e) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

[46 FR 8951, Jan. 27, 1981, as amended at 76 FR 270, Jan. 4, 2011]

Sec. 50.27 Documentation of informed consent.

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A*short form* written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

[46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]

Subpart C [Reserved]

Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of this subpart D.

Sec. 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in 50.1

and56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:

(a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.

(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(1) The clinical investigation involves no more than minimal risk to the subjects;

(2) The waiver will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the

permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under 50.51 or 50.52.

(2) Where clinical investigations are covered by 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

Sec. 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under 50.53 or 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.
Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

APPENDIX D: Declaration of Helsinki

(Taken from http://www.hhs.gov/ohrp/archive/irb/irb_appendices.htm#j6)

WORLD MEDICAL ASSOCIATION
DECLARATION OF HELSINKI

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care *(Clinical research)*

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects *(Non-clinical biomedical research)*

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

APPENDIX E: Nuremberg Code
(Taken from http://www.hhs.gov/ohrp/archive/nurcode.html)

II. The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

"Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.]