

POLICIES AND PROCEDURES

The Institutional Review Board is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities under the auspices of the University of Puerto Rico Medical Sciences Campus. The IRB reviews all human subject research conducted by faculty, staff, and students, regardless of the location of the research activity, source of funding, and whether the research is exempt under the Code of Federal Regulations for Protection of Human Subjects. The intent of the institutional policy to review all human subject research irrespective of location, source of funding, and exempt status is to foster high ethical standards in the conduct of research and to assure that uniform criteria are applied to protect the human subjects who take part in research.

ETHICAL PRINCIPLES

The University of Puerto Rico Medical Sciences Campus is guided by the ethical principles regarding all research involving humans as subjects, as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (entitled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research [the “Belmont Report”]) (Please see Attachment 1), regardless of whether the research is subject to Federal regulation or with whom conducted or source of support (i.e., sponsorship). All Institutional and non-Institutional performance sites for this Institution, domestic or foreign, will be obligated by this Institution to conform to ethical principles, which are at least equivalent to those of this Institution.

INSTITUTIONAL POLICY

All requirements of the Code of Federal Regulations will be met for all human subject research regardless of sponsorship, except as otherwise noted. Federal (all departments and agencies bound by the Federal Policy) funds may not be expended for research involving human subjects unless the requirements have been satisfied.

Except for those categories specifically exempted or waived, all research will be reviewed and approved by the Institutional Review Board (IRB). The involvement of human subjects in research will not be permitted until the IRB has reviewed and approved the research protocol and informed consent has been obtained from the subject or the subject’s legal representative, unless properly waived by the IRB.

The University of Puerto Rico Medical Sciences Campus assures that before human subjects are involved in nonexempt research, the IRB will give proper consideration to:

1. The risks to the subjects,

2. The anticipated benefits to the subjects and others,
3. The importance of the knowledge that may reasonably be expected to result, and
4. The informed consent process to be employed.

The IRB reviews research in accordance with current Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) regulations. The main purpose of the IRB is to protect the rights and welfare of human subjects who take part in research. More specifically, the IRB assures that:

1. Risks to subjects are minimized.
2. Risks to subjects are reasonable in relation to any benefits that might be expected from taking part in a research study and to the importance of the knowledge that may result.
3. Selection of subjects is fair and equitable.
4. Participation is voluntary and informed consent is obtained from each prospective subject or where appropriate, from the subject's legally authorized representative.
5. The research plan provides for monitoring the data collected to ensure the safety of subjects.
6. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Certification of IRB review and approval for all Federally sponsored research involving human subjects will be submitted to the appropriate Federal department or agency. Compliance will occur within the time and in the manner prescribed for forwarding certifications of IRB review to Federal departments or agencies.

Applications and proposals lacking definite plans for involvement of human subjects will not require IRB review and approval prior to award. However, except for research exempted or waived, no human subjects may be involved in any project until IRB review and approval has been certified. The IRB will review and recommend approval for involvement of human subjects research activities for which there was no prior intent for such involvement, but will not permit such involvement until the IRB's review and approval.

The University of Puerto Rico Medical Sciences Campus will ensure that any collaborating entities (i.e., those engaged in human subject research by virtue of subject accrual, transfer of identifiable information, and/or in exchange of something of value, such as material support [e.g., money, drugs, or identifiable specimens], co authorship, intellectual property, or credits) materially engaged in the conduct of non-federally sponsored research involving human subjects will possess mechanisms to protect human research subjects that are at least equivalent to those procedures provided for in the ethical principles to which this Institution is committed.

The Institution will comply with the requirements of the regulations regarding cooperative research projects. When research is conducted at or in cooperation with another entity, the Institution will not accept, for the purpose of meeting the IRB review requirements, the review of any other IRB.

This Institution will exercise appropriate administrative overview to ensure that the Institution's policies and procedures designed for protecting the rights and welfare of human subjects are being effectively applied in compliance with these regulations.

Applicability

Except for research in which the only involvement of humans is in one or more of the categories exempted or waived, all research involving human subjects, and all other activities which even in part involve such research, regardless of sponsorship, if one or more of the following apply:

1. The research is sponsored by this Institution, or
2. The research is conducted by or under the direction of any employee or agent of this Institution in connection with his or her Institutional responsibilities, or
3. The research is conducted by or under the direction of any employee or agent of this Institution using any property or facility of this Institution, or
4. The research involves the use of this Institution's non-public information to identify or contact human research subjects or prospective subjects.

All human subject research which is exempt will be conducted in accordance with: (1) the Belmont Report, (2) this Institution's administrative procedures to ensure valid claims of exemption, and (3) orderly accounting for such activities.

Responsibilities

Institution

The University of Puerto Rico Medical Sciences Campus acknowledges that it bears full responsibility for the performance of all research involving human subjects, including complying with Federal and local laws as they may relate to such research.

The Institution will ensure that, unless specifically exempted, all research will be reviewed and approved by the IRB. The involvement of human subjects in research covered by this policy will not be permitted until the IRB has reviewed and approved the research protocol ensuring that an informed consent is required and obtained in accord with and to the extent required by the CFR. Certification of the IRB's review and approval for all Federally funded research involving human subjects will be submitted to the awarding agency with the application of proposal for funding or as soon as approved by the IRB. Furthermore, the IRB's review of research on a continuing basis will be conducted at appropriate intervals but not less than once per year. Non Federally

funded research involving human subjects will be handled in the same manner, whereas certification of the IRB's review and approval for research involving human subjects will be submitted to the sponsoring Institution as approved by the IRB.

It is the policy of this Institution, that unless informed consent has been specifically waived by the IRB, no research investigator shall involve any human being as a subject in research unless the research investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

The Institution will require appropriate additional safeguards in research that involves: (1) fetuses, pregnant women, or human ova in vitro fertilization, (2) prisoners, (3) children, (4) the cognitively impaired, or (5) other potentially vulnerable groups. This Institution acknowledges and accepts its responsibilities for protecting the rights and welfare of human subjects in research.

This Institution is responsible for ensuring that no performance site cooperating in the conduct of research does so without Federal department or agency approval of an appropriate assurance of compliance and satisfaction of IRB certification requirements.

In accordance with the compositional requirements, this Institution has established the IRB listed in the attached roster (Please see attachment 6). Certain research supported by the U.S. Department of Education will be reviewed in accordance with the requirements of Title 34 CFR Parts 350 and 356 which require that the IRB include one person who is primarily concerned with the welfare of handicapped children or mentally disabled persons.

IRB members are appointed by the Chancellor of the University of Puerto Rico Medical Sciences Campus from the various sections of the University and from the community at large to ensure that the committee:

1. is sufficiently qualified to safeguard the rights and welfare of human research subjects; and
2. possesses the professional competence necessary to review a specific research activity, and 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 consists of at least 5 members (and alternates who attend meetings in their absence). The Compliance Officer is an ex-officio member of the committee.

The Institution will provide both meeting space and sufficient staff to support the IRB's review and record keeping duties.

The Medical Sciences Campus recognizes that involvement in research activities of any OHRP-recognized Cooperative Protocol Research Programs (CPRPs) will involve additional reporting and record keeping requirements related to human subject protection.

The Medical Sciences Campus is responsible for ensuring that it and all its affiliates comply fully with all applicable Federal policies and 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).

The Institution will maintain one IRB in accordance with all applicable regulations. The IRB will have the responsibility and authority in the Institution, its components and affiliates to review, approve, disapprove or require changes in appropriate research activities for the protection of human subjects.

This Institution encourages and promotes constructive communication among the IRB, research investigators, research administrators, department heads, clinical care staff, other Institutional officials, and human subjects as a means of maintaining a high level of awareness regarding the safeguarding of the rights and welfare of the subjects.

It will exercise appropriate administrative overview carried out at least annually to ensure that its practices and procedures designed for the protection of the rights and welfare of human subjects are being effectively applied and are in compliance with the established requirements.

The Institution will ensure that all research projects involving human tissues and biological substances which may present a hazard or biohazard to laboratory personnel be forwarded to the Institutional Biosafety Committee (Please see attachment 9).

The Office of Contracts, External Funds and Financial Administration (OCFA) will review all research grants; contracts and solicitations to ensure that proposed research projects could be performed in the Institution or affiliates. OCFA will ensure that Institutional commitments are obtained, and proposed research projects meet all federal and local regulations.

Division of Compliance (DC)

The Division of Compliance will receive from investigators all research protocols, which involve human subjects, keep investigators informed of the decisions and administrative processing, and return all disapproved protocols to them.

The DC is responsible for reviewing the preliminary determinations of exemption by investigators and for making the final determination. Notice of concurrence for all exempt research will be promptly conveyed in writing to the investigator. All nonexempt research will be forwarded to the IRB.

The DC will make the preliminary determination of eligibility for expedited review procedures. Expedited review of research activities will not be permitted where full board review is required.

The DC will review all research (whether exempt or not) and decide whether the Institution will permit the research. If approved by the IRB, but not permitted by the DC, the DC will promptly convey notice to the investigator and the IRB Chairperson. Neither the DC nor any other office of the Institution may approve a research activity that has been disapproved by the appropriate IRB.

The DC will forward certification of IRB approval of proposed research to the appropriate Federal department or agency only after all IRB-required modifications have been incorporated to the satisfaction of the IRB.

The DC is responsible for ensuring constructive communication among the research administrators, department heads, research investigators, clinical care staff, human subjects, and Institutional officials as a means of maintaining a high level of awareness regarding the safeguarding of the rights and welfare of the subjects.

The DC will arrange for and document in its records that each individual who conducts or reviews human subject research has first been provided with a copy of the MPA (Please see attachment 4), as well as with ready access to copies of 45 CFR 46 (Please see attachment 2), 21 CFR 50, 21 CFR 56 (Please see attachment 3), and regulations of other Federal departments or agencies as may apply, the Belmont Report, and all other pertinent Federal policies and guidelines related to the involvement of human subjects in research.

The DC will report promptly (within 72 hours) to the IRB, appropriate Institutional officials, the Office for Protection from Research Risks (OHRP), the Food and Drug Administration (FDA) and any other sponsoring Federal department or agency head:

1. Any injuries to human subjects or other unanticipated problems involving risks to subjects or others,
2. Any serious or continuing noncompliance with the regulations or requirements of the IRB, and
3. Any suspension or termination of IRB approval for research.

The DC will ensure that all affiliated performance sites that are not otherwise required to submit assurances of compliance with Federal regulations for the protection of research subjects at least document mechanisms to implement the equivalent of ethical principles to which this Institution is committed.

When the IRB accepts responsibility for review of research conducted by any independent investigator, the Division of Compliance will either: (a) obtain and retain a Non-Institutional Investigator Agreement (NIA) for CPRP activities (with copies to the investigator and the authorizing CPRP) or (b) obtain an Agreement for an Independent Investigator for review and approval by the appropriate Federal department or agency for non-CPRP activities to document the investigator's commitment to abide: (1) by the

same requirements for the protection of human research subjects as does this Institution(s) and (2) the determinations of the IRB.

The DC will ensure compliance with the requirements regarding cooperative research projects. For all Cooperative Amendments (CAs) the DC will forward the original of the required signed understanding to OHRP for approval and inclusion in this Assurance as an addendum.

When the DC determines that the Institution will not perform a research project, it will notify the IRB of the determination. The DC understand and agrees that a research project that has not been approved by the IRB cannot and will not be approved nor accepted by the DC, any other Institutional official nor by the Institutional authorized official.

Institutional Review Board (IRB)

The IRB will review, and have the authority to approve, require modification in, or disapprove all research activities, including proposed changes in previously approved human subject research. For approved research, the IRB will determine which activities require continuing review more frequently than every twelve months or need verification that no changes have occurred if there was a previous IRB review and approval.

IRB decisions and requirements for modifications will be promptly conveyed to investigators in writing. Written notification of decisions to disapprove will be accompanied by reasons for the decision with provision of an opportunity for reply by the investigator in writing.

Initial and continuing convened IRB reviews and approvals will occur in compliance with applicable regulations for each project unless properly found to be exempt by the DC. Continuing reviews will be preceded by IRB receipt of appropriate progress reports from the investigator, including available study-wide findings.

The IRB will observe the quorum requirements. The Institution's IRB has effective knowledge of subject populations, Institutional constraints, differing legal requirements, and other factors which can foreseeably contribute to a determination of risks and benefits to subjects and subjects' informed consent and can properly judge the adequacy of information to be presented to subjects in accordance with requirements.

The IRB will determine, in accordance with the criteria found at the Federal policies and guidelines for involvement of human subjects in HIV research, that protection for human research subjects are adequate.

The IRB will ensure that legally effective informed consent will be obtained and documented in a manner that meets the requirements. The IRB will have the authority to observe or have a third party observe the consent process.

Where appropriate, the IRB will determine that adequate additional protection are ensured for fetuses, pregnant women, prisoners, and children, as required by Federal regulations. The IRB will notify OHRP promptly when IRB membership is modified to satisfy requirements of 45 CFR 46.304 and when the IRB fulfills its duties under 45 CFR 46.305©.

Scheduled meetings of the IRB(s) for review of each research activity will occur not less than every 12 months and may be more frequent, if required by the IRB on the basis of degree of risk to subjects. The IRB may be called into an interim review session by the Chairperson at the request of any IRB member or Institutional official to consider any matter concerned with the rights and welfare of any subject.

The IRB will prepare and maintain adequate documentation of its activities in accordance with, and in conformance with requirements.

The IRB has the authority to suspend or terminate previously approved research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

The IRB will ensure effective input (consultants or voting or nonvoting members) for all initial and continuing reviews conducted on behalf of performance sites where there will be human research subjects. IRB minutes will document attendance of those other than regular voting members.

The IRB will act with reasonable dispatch, upon request, to provide full board review of protocols of OHRP-recognized Cooperative Protocol Research Programs (CPRP). The IRB will not employ expedited review procedures for CPRP protocols when they are to be entered into for the purpose of research. Although emergency medical care based on such protocols is permitted without prior IRB approval, patients receiving emergency care under these conditions will not be counted as research subjects and resultant data will not be used for research purposes.

Certifications of IRB review and approval will be forwarded by the IRB to the appropriate Federal department or agency for research sponsored by such departments or agencies.

The IRB assumes responsibility for ensuring conformance with special reporting requirements for any OHRP recognized Cooperative Protocol Research Programs in which the Institution participates.

Research Investigator

Research investigators acknowledge and accept their responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions.

Research investigators who intend to involve human research subjects will not make the final determination of exemption from applicable Federal regulations.

Research investigators are responsible for providing a copy of the IRB-approved informed consent document to each subject at the time of consent, unless the IRB has specifically waived this requirement. All signed consent documents are to be retained in a manner approved by the IRB.

Research investigators will promptly report proposed changes in previously approved human subject research activities to the IRB. The proposed changes will not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

Research investigators are responsible for reporting progress of approved research to the IRB, as often as and in the manner prescribed by the IRB on the basis of risks to subjects, but no less than once per year.

Research investigators will promptly report to the IRB any injuries or other unanticipated problem involving risks to subjects or others.

No research investigator will seek to obtain research credit for, or use data from, patient interventions that constitute the provision of emergency medical care without prior IRB approval. A physician may provide emergency medical care to a patient without prior IRB review and approval, to the extent permitted by law. However, such activities will not be counted as research nor the data used in support of research.

Affiliated Institutions and Investigators

Each performance site to this Institution that is involved in federally sponsored research activities must provide to the Division of Compliance an appropriate written assurance of compliance with the Belmont Report and the Federal Policy, to include Subparts B, C, and D of the 45 CFR 46 where appropriate (or equivalent protection if a foreign site), for review and approval, as specified by the sponsoring Federal department or agency (e.g., by OHRP for DHHS), prior to involvement of human subjects or expenditure of funds or other support to do so.

Each Institutional performance site must respond to a request by the Division of Compliance of this Institution for an Inter-Institutional Amendment, SPA, or CPA (as appropriate), whichever is most suited to the circumstances.

Each non-Institutional performance site (e.g., a private practice physician not otherwise an employee of this Institution) who is involved in human subject research of this Institution must respond to a request by the Division of Compliance of this Institution for either an Agreement for an Independent Investigator or a Non-Institutional Investigator Agreement, as appropriate, depending on the nature of the research activity.

INSTITUTIONAL REVIEW BOARD ADMINISTRATIVE REGULATIONS

Institutional Review Board Office

The Institutional Review Board Office is separate from the Institutional Review Board. The office provides the administrative support for the Board's functions. It serves as the liaison or communication center between the Board and the investigators submitting their research for IRB review. The IRB office has the administrative responsibility of documenting that all human research activities approved by the Board are in compliance with federal regulations and guidelines and with institutional policy.

Investigators should address all questions regarding use of human subjects or IRB actions to the IRB Office. Contacting individual IRB members or the IRB Chairperson directly will result in a delay, since that individual will have to refer the query to the IRB Office for documentation of the communication.

What Needs IRB Review?

Definition of Human Subjects

The IRB must review all proposed research where the investigational procedures involve the use of anything human (Please see attachment 5). This broad definition encompasses a wide variety of activities such as in vivo and in vitro studies, review of medical records, collection of data through surveys or observation, performance of blood tests, examination of existing pathological specimens, discarded tissue, or secretions, any use of investigational drugs or devices and randomized trials. The federal regulations give the following definition:

45 CFR 46 46.102(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 associate with the information) in order for obtaining the information to constitute research involving human subjects.

There is occasional confusion about research that is *exempt*. It has been mistakenly assumed that *exempt research* does not need IRB review. However, *exempt* means that it falls within a narrowly defined category of research needing administrative review rather than full board review.

Definition of Research

There is sometimes a question of whether a planned activity is *research* and therefore needs IRB review. The Code of Federal Regulations defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or to contribute to generalizable knowledge. Other criteria that can be used to determine whether a planned activity is research include:

- The collection of data with the intent to report them in scientific publications
- Use of a standard procedure or medication if it is influenced by any consideration other than the direct welfare of the patient, even if both therapies seem equal to the physician in charge (e.g., a selection between different though widely accepted therapies according to a predetermined plan such as randomization)
- Use of investigational drugs or devices

Innovative or newly-introduced therapies or procedures do not require IRB review and approval except when they involve *research* activities (e.g., the systematic collection of data with the intent to evaluate the effectiveness of the therapy, use of an experimental drug or device, or use of any procedure such as randomization which is not done solely for the benefit of the patient). When such therapies or procedures involve research, a protocol for their use must be reviewed by the IRB and cannot be initiated without IRB approval.

Who Needs IRB Review?

All research involving human subjects conducted by someone affiliated with the institution, or conducted by anyone at one of the institutions the IRB serves must be reviewed by the UPR MSC IRB.

Faculty, Staff and Students

IRB review is required to faculty, staff, and students who are investigators in human subject research conducted on or off-campus. An investigator is an individual who assumes responsibility for part or all of the actual conduct of a research study and/or the preparation of results. When a faculty or staff member serves as a consultant on a project, that is, as expert advisor only, IRB review of the research is not required.

Students proposing to engage in human subject research must have a faculty member as an advisor under whose supervision the research will be conducted.

Please note that when an employee of any type (faculty or staff, full time or part time, permanent or temporary), or a student conducts research at an institution that has its own IRB, approval is necessary both from the IRB at the site of the study and from the UPR MSC IRB. In addition, written documentation of the other IRB's approval is required by the UPR MSC IRB.

Clinical Faculty at the UPR MSC

Research conducted by clinical faculty is subject to review by the IRB if the research is within the course and scope of their university duties or conducted in the facilities of any of the institutions that the IRB serves.

Private physicians who are clinical faculty often perform ancillary roles in research sponsored by the UPR MSC, such as: recruitment and preliminary screening of patients, follow-up of patients, adjustment of medications, performance of tests, and collection of blood/urine samples. In such cases, a UPR MSC faculty member will serve as principal investigator in the conduct of the research and the IRB reviews the protocol in the standard manner.

Where primary responsibility is assumed by the clinical faculty member for the conduct of a study in his or her private office or in an outlying hospital or other facility, the research may be reviewed by the IRB if all of the following conditions are met:

1. the research is within the course and scope of university duties;
2. the individual has agreed to conform to all university policies governing research including review and approval by the IRB of the proposed research; and
3. the standards of the private office or other facility where the research is to be conducted are sufficient to assure that adequate facilities and expert professional care are available for a subject in the event of difficulties;
4. **Approval of the IRB (or administration if there is no IRB) of the institution where the research is to be conducted is documented; and the investigator:**
 - a. understands his or her responsibilities relating to the conduct of human research and agrees in writing to abide by all requirements imposed by the IRB;
 - b. certifies that he or she has professional liability insurance which is applicable to the study being performed; and
 - c. agrees to indemnify and hold harmless the University of Puerto Rico System, the System Board of Trustees, employees, legal representatives, successors and assignees of the University and the System against all loss or liability, damage, cost or expense arising out of claims and/or suits seeking damages for injury, disease, and other bodily harm to persons, or damage to property, alleged to have been caused directly or indirectly as a result of the research.

Non-Employees

Individuals who are not employees of the institutions covered by the IRB, but who use patients, staff, students or facilities of any of the institutions under the Multiple Assurance must have their proposed research reviewed by the IRB and obtain approval before beginning the study.

Types Of IRB Review

The IRB provides two types of review of proposed studies:

1. Administrative Review
2. Full Board review

The type of review a study receives depends upon the risks to the potential subjects posed by the research. These risks include the probability and severity of possible harm to the subjects' physical, psychological, social, or economic welfare.

Federal regulations define minimal risk: risk that is no greater in probability and severity than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. This definition of minimal risk serves as the benchmark to determine whether proposed studies are eligible for an expedited review or require the review of the full Board.

Research that is eligible for administrative review is termed either "exempt" or "expedited." Before preparing a protocol to submit to the IRB, the investigator should check with the IRB staff regarding the types of research that are eligible for administrative review. The sections that follow outline the specific criteria to be used to determine whether a study is eligible for exempt or expedited review.

Exempt Research

To assure protection of human research subjects, institutional policy requires that all protocols believed by the investigator to be exempt, be reviewed by the CD office to certify whether the research in fact qualifies as exempt and to identify the exempt category. While research activities in this category do not undergo full board review and continued monitoring, the IRB requires an annual status report to determine whether the nature of the research has been modified and whether it is ongoing. Research activities in which the only involvement of human subjects will be in one or more of the following categories are considered exempt:

(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. NOTE: Category (2) cannot be considered as exempt when a study uses subjects who are minors except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey or 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 of 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, by the Food and Drug Administration or approved by the Environmental Protection Agency or Food Safety and Inspection Service of the U.S. Department of Agriculture.

These exemptions do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization.

Expedited Review

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the

specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

Research 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 subjects, the amounts drawn may not exceed 550 ml in 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children [see NOTE for definition of children], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a 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 sub gingival 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 washing; (j) sputum collected after saline mist nebulization.

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

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subjects' 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).

(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: Children are defined in the HHS regulations as "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."

Full Board Review

Research which is not eligible for administrative review under the above criteria requires review by the full Board.

Submission Deadlines And Approval Procedures

Exempt Research

There is no submission deadline for research that meets the criteria for exempt research. To obtain IRB review of such research, send the IRB a letter with the following:

1. The title and purpose of the study
2. The population to be studied (i.e., age, sex, number of subjects, etc.) or source of information (medical records, existing specimens, discarded tissue, etc.)
3. The method of data/specimen collection (attach questionnaires, data collection sheets, etc.)
4. The approximate duration of time over which the study will be conducted
5. Procedures that will be used to maintain confidentiality of information, including whether data will be collected with patient identifiers
6. Consent document(s) if required,
7. Source of funding, and
8. Relevant portions of the grant application or sponsor's protocol, if funding is being sought

Written notification of the results of the IRB review of exempt research is sent to the investigator. All modifications of the research activities must be prospectively approved by the IRB office and an annual status report is required of exempt research.

Expedited Review

There is no submission deadline for research that meets the criteria for expedited review. To obtain IRB approval of such research, send to the IRB one completed copy of the following:

1. The research protocol and/or grant application, and
2. Addenda providing any required information that is not part of the protocol or grant, and
3. Consent document(s)
4. the General Information Sheet
5. the Signature Assurance Sheet

After two reviewers determine that the proposed research meets the criteria for expedited review, an approval letter indicating the investigator's responsibilities, the duration of approval, and the date of continuing review, is sent to the principal investigator. When the letter of approval has been received, a study may begin. The approval of expedited protocols is reviewed and endorsed at the next convened full Board meeting and is recorded in the minutes. While it rarely occurs, the board has the authority to question any of the expedited approvals.

Full Board Review

The Review Deadlines are set and disseminated for each fiscal year in August. The Review deadline is generally 10 days prior to the IRB meeting, but occasionally is assigned to a different day because of holidays. The IRB office must ensure that both the reviewers and the investigators have adequate time available to prepare and respond to review.

Because of the large number of research projects that are reviewed each month, the IRB must adhere to this timetable. No extensions will be granted and no exceptions will be made.

It generally takes 3-4 weeks from review to final approval, with all conditions met. This is an estimate and meant to serve only as a guideline for funding deadlines.

Applications which meet the appropriate deadlines and contain all essential elements are placed on the agenda for the next scheduled IRB meeting.

Each IRB member receives a copy of each of the applications for study prior to the meeting.

At the Board meeting, the reviewers act as primary and secondary presenters, summarizing the application and any issues raised during the review process. After the reviewers make their own recommendations for further clarification or revision, the discussion is open to the full board. Upon termination of the discussion, an assessment of risk to the subjects is made. Risk is categorized as "minimal" or "more than minimal." A motion is then made and a vote taken to: (a) approve the application as submitted; (b) approve the application contingent upon specific conditions; (c) table or disapprove the application. A majority vote is required for any IRB action.

Approval is given for a period of no more than one year. Continuing review of the study will be made at least annually but may be made at shorter intervals, depending upon the degree of risk to subjects.

The Chairperson conveys the decision of the board in writing to the investigator after the meeting:

Approved as submitted. A letter of approval is sent to the principal investigator indicating the investigator's responsibilities, the duration of approval, and the date of continuing review. The consent document is stamped with the official date of approval.

It is the responsibility of the principal investigator to provide notification of approval to funding agencies or other committees.

Conditional approval. A letter outlining necessary revisions and/or clarifications required for approval is sent to the principal investigator. When the conditions have been met (by having submitted an amended protocol, additional information and/or consent documents to the chair), administrative approval can be given by the Chairperson of the IRB without the amended application being seen again by the full board, and the study may begin. A letter is sent to the principal investigator indicating the approval date, the investigator's responsibilities, the duration of approval, and the date of continuing review. The consent document is stamped with the official date of administrative approval. Subjects may not be recruited nor involved in the study until unconditional approval has been given.

Tabled or Disapproved. The changes required in the protocol or questions raised by the board are significant and the investigator's replies will be reviewed at a subsequent full Board meeting. A letter outlining necessary revisions and/or clarifications is sent to the principal investigator. A revised application may then be submitted following the procedures and deadlines for new submissions. The "new" protocol application is reviewed by the IRB in the standard manner.

Approval of Other Committees

In addition to IRB approval, a research project may need the approval of other committees before it is implemented. If radioactive substances are to be used or the research subject is to be exposed to X Rays or other radiation for research purposes, approval must be obtained by the investigator from the Radiation Safety Committee. Submission of a protocol to committees other than the IRB is the responsibility of the investigator.

Frequently, other committees will require the principal investigator to make changes in a protocol or consent documents after they have been approved by the IRB. When such changes are made, the investigator must submit the changes to the IRB for approval. While the protocols and consent documents may vary between the sites, all documents to be used at the various sites must be approved by the IRB. Initiation of a study without final IRB approval of all modifications constitutes a violation of Federal regulations and institutional policy.

Approval by Other IRB

The approval of faculty, staff or students' research by another institution's IRB cannot substitute for the requirement to have the protocol reviewed by the UPR MSC IRB.

Preparing An Application For IRB Review

The essential elements of the IRB application are:

1. the research protocol or appropriate parts of the grant application,

2. addenda providing any required information that is not part of the protocol or grant,
3. consent document(s) English and Spanish versions if applicable
4. the Signature Assurance Sheet
5. the General Information Sheet

It is essential that the entire application be prepared carefully and completely according to the guidelines on the forms and in this handbook. They become permanent IRB records and are subject to inspection and review by various funding agencies and, where applicable, by the FDA and DHHS.

Because funding sources have different application requirements, IRB application forms are designed to allow flexibility in the format of materials submitted for review. Certain elements are required but may vary in form.

Title of Study: The title must be consistent throughout the application, including the consent document, and should not differ from a grant or sponsor's protocol.

Principal Investigator: Indicate the name of the individual who assumes responsibility for the overall conduct of the study and preparation of results. The principal investigator also will be the responsible correspondent. If the principal investigator is a student or resident, include the name of the faculty advisor.

Co-Investigators: Indicate the name(s) of the individual(s) who assume(s) responsibility for part of the actual conduct of the study and/or preparation of results.

Signatures: Include signatures of the principal investigator, and department chair. The signature of the department chair warrants that he/she is aware that the principal investigator intends to conduct the proposed research in his/her department.

Original signatures are required. If one of those whose signature is required is not available at the time of submission, please note the following: Use of a rubber stamp is not permitted. If the principal investigator is not available, a co-investigator may sign on behalf of the principal investigator. If the division chief is unavailable, a deputy or acting chief may sign. If the chairman is unavailable, the signature of a deputy chair or an acting chair is acceptable. The signature of administrative, non-scientific personnel such as the assistant to the chair, is not acceptable.

Record of Institutional Review Board Action: Do not complete this section since it is for the use of the IRB staff. The IRB Protocol Number will be assigned by the IRB and will appear on the letter sent to the principal investigator informing him/her of the board's action. All correspondence concerning a protocol must refer to this number as it is the preferred method by which study protocols are identified in the IRB files.

Research Protocol

The investigator must supply a complete description of the research plan. In many cases, this information may be presented by using appropriate sections of grant applications or protocols supplied by sponsors. When required elements are not present in the grant or the sponsor's protocol, it may be supplemented by an addendum containing the additional information. When the research involves a new drug or device, a copy of the investigator's brochure should also be included.

Consent Documents

Consent documents are used in the process of obtaining informed consent to ensure all required information is given consistently to all potential subjects. It serves to document that the consent process took place to the satisfaction and understanding of both the subject and the investigator.

Informed Consent

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representatives. Exceptions must be approved by the IRB.

The consent process involves explaining a study to the prospective subject, ensuring that the individual has understood the information, giving that person adequate opportunity to consider all options, responding to their questions, and obtaining the individual's voluntary consent to participate. To be effective, the consent process must provide an opportunity for the investigator (or designee) and the individual to exchange information and ask questions--both at the time of recruitment and throughout that person's participation. It may involve the use of charts, models, video tapes and other audio visuals that may assist in communicating the procedures and processes that will be part of the study. For complex protocols, incorporation of diagrams and flow charts into the consent document itself is encouraged to improve the clarity and description of the research procedures and possible treatment assignments.

The consent document is a legal document containing sufficient information to allow the prospective research subject to make an informed decision about whether or not to participate in the research and ensures that adequate information is given to the subject in the process of obtaining consent. It is not intended to be a protection for the investigator and does not constitute any waiver of liability. The signed consent document provides documentation of a subject's consent to participate in a study.

The IRB must approve all consent documents to be used. Approval must also be obtained from the IRB for each modification made in the form thereafter, before instituting the change. The version of the consent document being used should match exactly with the version given final IRB approval in the protocol file. The IRB will stamp and date each approved version of the consent document. The investigators are encouraged to use the stamped and dated copies to assist them in assuring the appropriate version is in use.

Guidelines for preparing a consent document follow.

Required Elements

Each of the following points must be covered in the consent document, except in cases where the point is irrelevant to the research:

1. A statement that the study involves research, an explanation of the purpose of the research and why the subject is asked to take part.
2. A description of procedures and identification of any procedures which are experimental. For example, the description of procedures should include the length and frequency of hospitalizations; number, frequency, and length of clinic visits; the total amount of time a subject should expect to devote to the study; names and types of medication; types and number of tests; amount of blood to be drawn; use of questionnaires; special diet; withholding of standard treatment; follow-up studies; and randomization, use of placebo, double-blind, or cross-over methods. In the case of patient subjects, state clearly which procedures are experimental and which procedures would be performed for medical reasons if the patient were not a research subject.
3. A description of any reasonably foreseeable risks or discomforts to the subject, their frequency and severity. These may include drug side effects, hazards of procedures, withholding therapy of proven value, financial risk, loss of privacy, or possible detection of genetic predisposition to a disease. Describe what will be done to minimize risks, counteract side effects, and which side effects might be irreversible.
4. A description of any benefits to the subject or to others which may reasonably be expected from participation along with a disclaimer that the investigator cannot guarantee there will be any benefit derived from taking part in the study.
5. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. It is not necessary to provide a full account of the risks and benefits of standard alternative treatments in the consent document. In some cases, it may be appropriate to state that one reasonable alternative is to choose not to accept any therapy designed to produce cure or remission.
6. A statement describing the extent to which confidentiality of records identifying the subject will be maintained. FDA and sponsor inspection of records in studies involving drugs and devices should be explained. The means of disclosure of information obtained during the study should be described, e.g., publication, entry in medical records, or transmission to another physician and assurance that publication will not lead to personal identification.
7. An explanation that medical treatment is available if a research-related injury occurs. However, if a company or agency sponsoring the research agrees to

provide for additional treatment and/or monetary compensation for injuries, this should be included in the consent document.

8. A statement about any costs for which the subject will be responsible and identification of any which are due solely to research. If the research activity will add substantially to the cost of patient care, state this clearly and specifically. It is important to explain to the subject/patient that they might have to pay more money for taking part in the study than they might pay for alternative treatments available and that their physician will discuss with them the costs of the treatment(s) offered through the study as compared to what other treatment might cost. The same applies when there is a disparity of costs between treatment arms (e.g. chemotherapy vs. bone marrow transplant) in the same study. Where applicable the subject should be informed that insurance carriers might not cover costs of research related procedures.
9. A statement of the amount of compensation to be paid to the subject for participation in the research, approximately when they will receive the compensation and the manner in which it will be pro-rated in the event the subject does not complete the study.
10. Identification including the full name(s) and 24-hour phone number(s) of the investigator(s) the subject may contact for answers to questions about the research and the research subject's rights, and whom to contact in the event the subject believes that he or she has sustained a research-related injury. This should include the Institutional Review Board as an agency prepared to identify the patients' rights.
11. A statement that participation is voluntary, and that the subject may refuse to participate or may withdraw from the research at any time without penalty or loss of benefits to which the subject is otherwise entitled. When appropriate, subjects should be assured that they will still receive standard treatment if they decide not to participate or to withdraw. They should also be assured that a decision not to participate will not adversely prejudice future interactions with the institution; this is particularly important when a dependent relationship exists between subject and investigator, such as physician-patient, employer-employee, or faculty-student. If withdrawal may be dangerous to a subject (for example, abruptly stopping medication that should be tapered), the danger must be explained and the subject should be told not to withdraw without first discussing it with the investigator.

Optional Elements

The following additional elements of informed consent should be included when appropriate:

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

2. Anticipated circumstances under which the subject's taking part may be terminated by the investigator.
3. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue to take part will be provided to the subject.
4. A statement that the investigational drug or device may not be available after the study period.
5. A description of any plan to bank biological specimens or perform genetic analyses, including potential risks.

FORMAT

Language

The consent document should be worded in second or third person active tense (i.e. the participant...) and written in a language that the subject can be expected to understand (simple enough for a sixth grade student), and should not sound nor be coercive.

Two or More Consent Documents

It sometimes is necessary to use two or more consent documents when procedures are to be performed on subgroups of subjects or when reasons for subject selection differ. The most common example of this situation is studies which involve both patients and normal subjects or a treated and a control population. If there is more than one consent document, place a label after the title indicating the subject population to which each is addressed.

Technical Elements

At the top of the first page, the consent document should bear the title of the study, and the name of the institution. Pages should be numbered "1 of 4," "2 of 4," etc. At the end of the consent document there should be statements that the subject will be given a copy of the form to keep. Spaces should be provided for: (a) the signature of the subject who consents to take part; or in the case of a minor, of the parent or guardian who consents on behalf of the subject and a line for the assent of the subject if age 6 or older; (b) the signature of the individual who witnesses the subject's signature; (c) the signature of the investigator or other approved person who enrolls the subject. The witness and the person enrolling the subject cannot be the same person. If someone other than an investigator is to obtain consent, IRB approval is necessary. Additionally, the signature of the witness attests only to the signature of the subject. Unless specifically identified and approved by the IRB, the witness does not act as a consent auditor.

Special Considerations

Banking or Saving Biological Specimens or Creation of Permanent Cell Lines for Future Use.

When the research includes a plan to bank or save biological specimens for future use, the following must be addressed in the protocol and the consent form:

- (i) provide an explanation regarding the purpose of obtaining/saving the sample(s) and indicate not only how they will be used in the immediate research effort, but state that samples will be stored or cell lines will be established from them with the intent to use them in other future research;
- (ii) describe how the subject's confidentiality and privacy will be safeguarded first in terms of how the physical samples and records will be handled in the lab and then how they will be handled when the research is presented or published;
- (iii) state who has control over the sample once it is stored in the laboratory (the sample donor or the investigator) and where there exists a possibility of something being developed of commercial value, whether the sample donor may share in the expected profits;
- (iv) if the subject will be able to later withdraw his/her sample from further study, explain what subject should do to make this happen;
- (v) give an estimate of the period of time the sample will be kept and used in future research;
- (vi) state whether subject will be given any results of the research being done now and or from future research done with their sample(s);
- (vii) state whether there is any possibility of third party access to information learned from the samples; and
- (viii) clarify whether the subject would be contacted to ask for consent for future research endeavors using his/her specimen or to ask for additional information.

Genetic research

While much genetic research is in very early stages and would not yet have clinical implications, the eventual goal of most genetic research is to discover whether there is a genetic cause for a disease state or a genetic factor that could have treatment implications. DNA can be derived from many easily obtained biological specimens, so the risk associated with genetic research is NOT a physical risk. It is a social and psychological risk. Genetic information pertains to the most personal aspects of individuals' lives and may have implications for family members as well. The research protocol and the consent form must clearly state what type of information will be gained

about the disease, its treatment, about the people who have the disease, about the individual tested, about their families and about their children. Subjects need to understand what the implications and what the potential consequences are of obtaining the information sought. A subject might very well want to be part of the laudable effort to discover the gene that may cause Alzheimer. However, it may never occur to that subject that if it is determined he/she has the Alzheimer's' gene, it might mean that he/she would likely develop the disease. Furthermore, if the results of the genetic research somehow become part of the subject's medical record and the medical record is later reviewed by the health insurance company, and the insurer gives the information to the employer, it could jeopardize the subject's career and insurability. In pedigree studies, non-paternity and non-maternity may also be unexpectedly revealed, changing family relationships forever. Even when DNA is used in research without identifiers, some argue that DNA can never be truly anonymous since each person's DNA is unique, like a fingerprint. Researchers planning genetic research must address the potential risks to the subjects and their loved ones, state how confidentiality will be safeguarded, indicate how results will be handled, specify the disposition of the biological specimen once the immediate research project is complete and clearly state what information will or will not be shared with the subject.

Guardian Consent

Unless he/she is also a court appointed guardian or has durable power of attorney to consent for medical treatment, a "next-of-kin" usually cannot give consent for research on an adult subject. Permission for a child to take part in research must be obtained from a parent or legal guardian. Unless waived by the IRB, children who are capable of understanding their involvement in a study should be given the opportunity to assent to the research by signing the assent document in addition to their parents, having been informed of the nature of the project. Generally, age 6 is accepted as the age at which assent is sought. Emancipated minors (those under 21 years of age and married, or those for whom minority status has been court-removed) may consent on their own to take part in research. Although some minors may consent to certain types of medical treatment, there is no legal precedent that they, by themselves, may consent to take part in research.

Assent

Adequate provisions must be made for soliciting the assent of children, when the children are capable of providing assent. The ages, maturity, and psychological state of the children involved should be taken into account. Generally, age 6 is accepted as the age children should give assent. If the 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, assent of the children is not a necessary condition for proceeding with the research. Regarding the involvement of adults who are mentally disabled, in addition to the consent of a legally authorized representative or guardian, the feelings and expressed wishes of the incompetent person should still be respected. Investigators should both inform the subject and solicit his/her assent to take part in the study.

Deception

The IRB recognizes that in some cases, informing the subject of the hypothesis being tested may result in a biased response. Under these circumstances, the nature of some studies requires that the full purpose not be revealed to a subject until the study has been completed. Such intentional withholding of information may be permitted if the subject is informed that this is the case and agrees. Plans for when and how complete information will be shared with the subject should be disclosed in the consent document.

Pregnancy

If women of childbearing potential are included in a study and there are risks to the woman or fetus, the consent document should describe the test that will be done to determine whether the potential subject is pregnant, the need for contraceptive measures, and known risks of the research to a pregnant woman and fetus. If appropriate, the form should state recommendations about continuation of a pregnancy should the subject become pregnant, and who will bear financial responsibility for the termination of a pregnancy, should the subject and physician determine that this is the alternative of choice.

Screening Studies to Identify Eligible Subjects

If a procedure is to be performed solely for the purpose of identifying a population of research subjects, consent for the screening test and/or process is required. Often, it is appropriate for the screening to be presented in a separate consent document describing the screening procedure and stating that its purpose is to determine eligibility for participation in further studies. A separate consent document for the actual study would then be signed by individuals found to be eligible. In such situations, at the time the subject is enrolled for the screening procedures, the prospective subjects should be shown the document they will be asked to sign if they prove to meet the criteria for further study.

Distribution And Storage Of Signed Consent Documents

A complete copy of the consent document must be given to each subject. A copy with original signatures must be retained in the investigator's file for a minimum of five years after completion of the study.

Guidelines For Subject Consent In Survey Research

Survey research involving the use of self-administered questionnaires and telephone and face-to-face interviews generally places subjects (respondents) at minimal risk. In addition to possible invasion of privacy and disruption of normal routine, the risks can include possible legal risks, possible inconvenience, embarrassment, and other kinds of

psychological discomfort. Such risks may become more than minimal when sensitive information (such as sexually transmitted diseases, AIDS, alcohol and drug abuse) is requested.

Self-Administered Questionnaires

A cover letter containing the following information should accompany a self-administered questionnaire:

1. An explanation of the purpose of the questionnaire
2. An explanation of how and/or why the subject was asked to participate
3. A statement of the amount of time the questionnaire will require
4. A description of any stresses associated with sensitive information elicited
5. A description of any benefits reasonably to be expected
6. An offer to answer any inquiries concerning the questionnaire
7. An instruction that the subject is free to refuse to fill out the questionnaire
8. An assurance of confidentiality, including how confidentiality will be maintained

In the instance that there will be no way of tracing respondents, return of the questionnaire to the investigator will be considered to be adequate informed consent provided the cover letter and contents of paragraph (1), above, accompanied the questionnaire.

Telephone and Face-To-Face Interviews

Whenever possible, a letter should precede an interview to inform the subject of the impending interview. The letter should contain the following information:

1. An explanation of the purpose of the interview and the kinds of questions to be asked
2. An explanation of how and/or why the subject was chosen to participate in the study
3. A statement of the amount of time the interview will require
4. A description of any benefits reasonably to be expected
5. An instruction that the subject is free to discontinue the interview at any time without prejudice
6. An assurance of confidentiality

At the beginning of the interview, the information contained in the letter should be told to the subject again by the interviewer.

Procedures for selection and training of interviewers should be described in the protocol. This should include the number of interviewers to be used, method(s) of recruitment, their familiarity with the community/population to be studied, the language in which the interview is to be conducted, and method of approaching subjects.

In the instance of telephone interviews, and assuming that the information letter is part of the process, the oral consent of the interviewee to continue the interview will be considered to be informed consent.

In the instance of face to face interviews, the informed consent document should be in writing. Informed consent should be obtained prior to the interview. The signatures of the subject, the interviewer, and the responsible investigator should be contained in the consent document. Like the letter and spoken introduction, the informed consent document should include all the information listed in items 1 through 6 above.

Waiver Of Requirement For Signed Consent

The IRB may waive the requirement of signed consent in some circumstances, and may require instead that a written statement describing the research be given to the subject. Such a waiver may be given when one of the following conditions exist:

1. The only record linking the subject and the research would be the consent document and the principal risk would be 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.
2. 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.

Recruitment And Selection Of Subjects

The Belmont Report describes how the principles of respect for persons, beneficence, and justice are relevant to research involving human subjects. Justice in particular relates to the selection of research subjects. The selection process needs to be scrutinized in order to determine whether some classes (e.g. welfare patients, 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. Whenever research 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.

The selection of subjects must be fair. Potentially beneficial research should not be offered only to some patients who are pleasant to work with; likewise, higher risk or research with no potential benefit to the subjects, should not be targeted only at "undesirable" populations. 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 under exceptional conditions.

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.

Screening Studies To Identify Eligible Subjects

Minor procedures involving little or no risk, may be performed for the purpose of identifying a population of research subjects. Consent is required.

Medical/Dental And Other Record Review To Identify Potential Subjects

It is permissible for an investigator to perform a chart or record review to obtain names and other identifying information for recruiting purposes. When a patient enters the teaching institutions for care, the standard release form states that records may be used for research purposes. Recruitment should be in a sensitive manner and the source of the information should be identified. For most studies, it is appropriate to include the primary physician or caretaker in the communication link with the patient.

If recruitment involves contacting in-patients or out-patients (or former patients) for participation in research, the activity must be described in the protocol and IRB approval is required prior to contact. Authorized investigators who had no role in treatment of the patient and whom the patient does not know, should describe the recruitment methods in the protocol and assure that the patient's responsible (primary) physician will obtain permission from that patient. If this is not feasible, an explanation and justification should be provided in the protocol for evaluation by the IRB.

When sending letters to recruit potential subjects identified through a chart review, it may be necessary to have the physician responsible for the patient (or the agency or institution where the chart review was done) co-sign the letter. The investigator should avoid contacting the patient directly (without the involvement of the patient's responsible physician) unless the investigator is known to the patient or the family, or would be

recognized by the patient as having had legitimate access to the information (medical chart) from which the patient's name had been obtained.

It is a breach of confidentiality to release names from research records. Release of subject's names must be at the voluntary discretion of the subject. Therefore, if investigator "B" wishes to recruit people from investigator "A"'s study population, investigator "A" must make the contact and ask interested persons to get in touch with investigator "B". Investigator "A" may not release the names of subjects to investigator "B".

Solicitation Of Subjects Through Advertisements

The use of advertisements (e.g., notices on bulletin boards, paid and unpaid newspaper solicitations, solicitation by electronic mail, WEB sites, letters to private practitioners, signs, or pamphlets, etc.) soliciting volunteers for research must have IRB approval. Such advertisements are an extension of the informed consent and subject selection process.

The IRB reviews advertisements to determine that (1) they are neither misleading nor coercive to potential subjects; and (2) in treatment protocols, no claims are made, either explicitly or implicitly, that a proposed treatment is safe and effective or equivalent or superior to any other treatment.

Advertisements should contain the following:

1. The name and address of the investigator
2. The purpose of the research
3. In summary form, the eligibility criteria
4. A straightforward, truthful description of the benefits, if any
5. The location of the research and the person to contact for additional information

Submission and approval procedures:

1. Identify method(s) of advertisement for research subjects in the protocol.
2. Submit bulletin board notices for IRB approval prior to posting. The IRB will return the advertisement with a dated IRB approval stamp. Subsequent changes in the content of an advertisement must be approved by the IRB.
3. If you plan to advertise in a newspaper, a WEB site, or other media advertisements, submit the text or a printed copy of the WEB information or other item for IRB approval. Solicitation of subjects within the context of a published or broadcast "news" release is not appropriate.
4. Submit other forms of advertisement (e.g., electronic mail, letters to private practitioners, letters to potential subjects, etc.) for IRB approval.

Finder's Fees

A proposed recruitment method which involves offering cash and/or tangible non-cash incentives to residents, fellows, private physicians, or others (i.e., finder's fees) is not permitted by institutional policy and cannot be approved by the IRB.

Food And Drug Administration Regulations

In addition to the requirements imposed by DHHS which form the basis of these Guidelines, the Food and Drug Administration also has regulations involving IRB review, informed consent and protection of human subjects. These regulations apply to all studies of test articles the results of which will be submitted to the FDA. Most of the provisions are identical to those in the DHHS regulations discussed in the general sections of these Guidelines but there are some additional requirements specific to the FDA, e.g. the requirement to report adverse events and provisions for emergency use of investigational drugs or devices.

FDA regulations refer to those items that they regulate (drugs, medical devices, biologicals, radiopharmaceuticals, food additives, and so on) as "test articles." It is frequently difficult for investigators to determine whether FDA regulations apply to their plans to use or study an "article." When in doubt, consult the IRB. In general, any plan to use an "article" that has not been approved by FDA for commercial distribution for use in humans will be covered by FDA regulations. In such cases, the industrial sponsor (or occasionally the individual "sponsor-investigator") of the "article" has the obligation to file with FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) or, in the case of devices, an IDE (Investigational Device Exemption).

In some cases, use of "articles" for either research or practice purposes may be covered by FDA regulations even though FDA has approved commercial distribution of the "article." For example, use of an approved drug for an indication or in a population not mentioned on the FDA-approved package label may be subject to FDA regulation. This would be the case if data were being developed in connection with the new use of the "article" to support an application to the FDA for a change in the package label.

Physicians who plan to use "articles" in ways that differ substantially from those identified on the package label should contact the firm that distributes the "article" in order to learn whether it wants the physician to develop data that might be used to support an application to the FDA for a change in labeling. If so, the industrial sponsor will usually choose to file an IND (or IDE) and all FDA regulations will be applicable.

Even if FDA regulations are not applicable, research involving investigational practices must conform to IRB guidelines.

Consent Form

Subjects must be informed that their medical records may be subject to review by agents of the FDA and, in some cases, by agents of the industrial sponsor.

Special Requirements

Research data reporting forms are to be modified so that no names, initials or other identifiers are used. Separate research code numbers should be used to identify individual subjects and only the investigators should have the means to link the code numbers to identifiable patients.

Inspections

Various federal agencies such as the FDA, the NCI and others have the authority to inspect medical records of patients or subjects involved in research studies in which these agencies have an interest. Because of the serious legal questions involved in federal access to information unrelated to research, investigators should call the Compliance Officer before showing medical records to any inspectors.

Investigators should contact the IRB as soon as they receive notice of an inspection or audit by a federal agency.

Investigators working on FDA-regulated studies are strongly encouraged to keep all data, notes, and consent forms as "research records" that are separate from the medical records. When FDA personnel arrive to inspect records, they may -- in the interests of protecting the patient's privacy -- be given these records rather than the medical chart.

Documentation

FDA regulations state that an investigator must maintain the records of drug disposition, signed consent documents, case report forms, all correspondence, dates of monitoring visits, and supporting documentation, for a period of two years following the date a New Drug Application is approved or until two years following the notification by the sponsor that the clinical investigations have been discontinued. The investigator may withdraw from the responsibility to maintain records and transfer custody of the records to another faculty or staff person who will accept responsibility for them. Notice of a transfer must be given to the FDA not later than 10 working days after the transfer occurs. A copy of that notice should also be sent to the IRB.

Responsibilities Of The Principal Investigator For Research In Progress

The final letter of approval sent to the principal investigator outlines the continuing responsibilities that the investigator has to the IRB while the research is being conducted. These responsibilities include:

1. Conducting the study only according to the protocol approved by the IRB;
2. Submitting any change(s) to the protocol and/or consent document(s) to the IRB for review and approval prior to the implementation of the change(s);
3. Ensuring that only persons formally approved by the IRB enroll subjects;

4. Reporting immediately to the IRB any severe adverse reaction or serious problem, whether anticipated or unanticipated;
5. Reporting immediately to the IRB the death of a subject, regardless of cause;
6. Reporting promptly to the IRB any significant findings that become known in the course of the research that might affect the willingness of subjects to participate in the study or, once enrolled, to continue to take part;
7. Submitting a Progress Report at intervals designated by the IRB (but no less than once a year);
8. Notifying the IRB when the study has been completed and to submit a final report.

The procedures for carrying out responsibilities (2), (4), (5), (6) and (7) are described in the sections that follow.

Protocol Modifications

Minor changes to an approved study can be approved administratively by the IRB Chair. A letter specifying the changes, the rationale for the changes, and (if applicable) a revised consent document should be sent by the principal investigator to the IRB office. After approval by the IRB Chair, an approval letter and the validated consent document will be sent to the principal investigator. The change may be implemented as soon as administrative approval has been given. The administrative approval of the change is reviewed and endorsed by the full Board at the next convened meeting.

In general, modifications or addenda that do not result in increased risks to human subjects may be considered minor and be eligible for administrative review. However, the IRB Chair may determine that the proposed change is more than minor and require full Board review. Each request will be judged on a case-by-case basis.

Reporting Adverse Experiences And Deaths

Anticipated adverse experiences. Adverse experiences that have been anticipated in the protocol, such as reactions to drugs, do not have to be reported to the IRB unless they are unexpectedly serious, life threatening, or fatal.

Serious and unexpected adverse experience or death. An unanticipated adverse experience or death occurring during the course of a research project, regardless of cause, must be reported to the IRB immediately (within 24 hours). Initial notification of the event can be made by telephone but must be followed promptly (within 5 days) with a written report, using a "Unanticipated Adverse Event Report" Form.

The FDA reporting requirements are similar. The FDA defines a "serious and unexpected adverse experience" as any unfavorable event associated with the use of the drug, whether or not it is considered drug related.

Serious means an adverse experience that is life threatening, permanently or severely disabling, or requires an emergency room visit or inpatient hospitalization.

Unexpected means an adverse experience that is not listed in the current labeling or investigational use data. This includes an event that may be symptomatically and pathophysiologically related to an adverse reaction listed in the labeling or protocol, but which differs because of greater severity or specificity.

Serious and unexpected adverse experience include:

1. Any unexpected event, injury, toxicity, or sensitivity reaction or any unexpected incidence or severity associated with clinical use; and
2. Any unusual failure of drug to exhibit its expected pharmacological activity.

Upon receipt of a Report of Adverse Experience or Report of Death, the IRB decides whether further investigation of the event is required. In some cases, an investigator may be required to suspend a study pending the outcome of IRB review. It is the responsibility of the investigator to inform the sponsor of the investigation and the FDA of the occurrence of unanticipated adverse reactions, death, or serious adverse experience.

Reapproval Of Protocols

(Continuing Review)

When a study is first approved by the IRB, the duration of approval is established. By regulation, approval can be given for a period of no more than one year. Depending on the degree of risk to subjects, approval may be given for shorter periods (e.g. semi-annual, quarterly, or after a number of subjects have been enrolled). A study cannot be conducted for longer than this specified period unless a progress report has been submitted and the protocol has been re-reviewed and approved by the IRB.

Progress Report - Prior to the expiration date of a protocol, the principal investigator must submit a progress report to the IRB. The IRB office will send the investigator a progress report form as a way of notifying him/her that a report is due. Information provided in the Progress Report and copies of consent documents currently in use are reviewed by the IRB with the original protocol using the same criteria used at initial review. Special attention is paid to determining whether the protocol has been followed, new information was discovered, whether the number of subjects is within approved limits, reasons for subjects not enrolling or not continuing in the study, or whether any unanticipated adverse experiences or deaths occurred during the investigation.

Progress Reports must be submitted to the IRB as long as any of the research activities described in the protocol are being conducted. For example, if all subjects have completed a study and only data are being analyzed, the study is still "active" because research activities that may effect the risk assessment are still being carried out.

If a study is completed or terminated before the expiration date (or date of next IRB review), the investigator must submit a completed Progress Report to the IRB.

If the progress report is not submitted in a timely fashion, the IRB approval of the study may expire while the continuing review is in progress. If this occurs, new subject enrollment and all new study activity must be suspended until IRB reapproval has been obtained.

Failure to submit the progress report and obtain reapproval will result in the IRB taking action to inactivate the study protocol. Subsequent reactivation would require complete resubmission to the full IRB as a new study.

Terminating Faculty, Staff or Students

For those studies being discontinued when the principal investigator leaves, a formal, written final report must be filed with the IRB. The IRB's Progress Report form may be used for this.

To comply with FDA and other applicable regulations and future requests for audits or inspections, records that completely document the research study must be left in the department where the study was conducted.

Emergency Use Of Experimental Drugs Or Devices

The use of an experimental drug or device for the benefit of a single patient may be approved without delay by the Chair of the IRB provided an emergency situation exists. The following conditions should exist for a situation to be considered an emergency:

1. The patient is suffering from a life-threatening condition that needs immediate treatment.
2. No acceptable alternative for treating the patient is available.
3. Because of the immediacy of the need to use the drug or device, there is not time to use existing procedures to obtain FDA or IRB (full board) approval.

Requests for emergency use of a drug or device can be made when an IRB-approved protocol exists, but the patient does not meet all eligibility criteria for enrollment (i.e., protocol deviation).

When an approved research protocol does NOT exist, an experimental drug or device can be used on this basis only once and a protocol must be submitted to the IRB within five days. If an investigator anticipates the need to use the drug or device additional times, a protocol must be submitted to the IRB for approval. Data from these activities may only be counted toward research to the extent required by FDA regulations.

Approval to provide emergency medical care for one patient does not constitute IRB approval of the protocol. All research protocols must receive full IRB review and approval prior to implementation.

To request approval for a one-time emergency use, send a letter to the IRB, detailing the following:

1. The patient's name and age
2. Physical condition
3. Justification for use of the experimental drug or device (e.g., documentation that no available alternative therapy exists)
4. Therapeutic plan (e.g., dose, mode of administration, duration of planned therapy)
5. IND/IDE and the name of the sponsor that is providing the drug or device
6. The name of a physician uninvolved in the patient's care who concurs that the drug or device is needed for a life-threatening situation
7. The name of the hospital in which the patient is to be treated, and
8. A proposed consent document that meets the criteria described in Section I.

In extreme emergencies (minutes or hours), an investigational drug or device may be used without IRB approval provided:

1. The investigator and an uninvolved physician certify in writing in the patient's medical record that the drug or device is needed for a life threatening situation;
2. The patient or the patient's legal representative signs a consent document that meets the criteria, except when the subject is unable to communicate consent and there is no time to obtain consent from the subject's legal representative;
3. If an IND/IDE exists, the sponsor is notified of the emergency use of the drug or device;
4. If an IND/IDE does not exist, the FDA is notified of the emergency use of the drug or device; and
5. A letter describing the situation and a copy of the signed consent document are submitted to the IRB within five days.

Following the emergency use of a drug or device, a written report of the patient's status should be submitted promptly to the IRB.

The Conduct Of Human Subject Research Without Prior Review By The IRB

From time to time, the IRB is made aware of research using human subjects that is being conducted without IRB review and approval of the research protocol. The sources of this information and the procedures that are followed when such information becomes available are outlined below.

Sources Of Information And Disposition Of Reports

The IRB occasionally discovers that human subject research which has not been reviewed by the IRB is being conducted. Investigators may report to the IRB themselves about unapproved human subject research in which they are involved. Other reports are received from faculty, staff, subjects, and anonymous persons.

Reports may be oral or in writing and should include as much pertinent factual data as possible. Reports are transmitted immediately to the Director of the IRB (or to the IRB Chair).

Determination Of Alleged Infractions Of Institutional Policy

The Chair of the IRB interviews the investigator to seek additional information to help determine whether or not an infraction of institutional rules has occurred. Emphasis in the interview is placed on fact finding.

If it is determined by the Chair of the IRB that no infraction has occurred, no further action is taken.

If it is determined that an infraction has occurred, the investigator is notified in writing of the procedures he or she must follow to comply with institutional policy regarding the review of human subject research. The procedures are outlined below.

Documentation And Review Of Non-Approved Research

Exempt Research

The investigator is required to suspend the exempt research and, if the investigator plans to continue the research to submit a protocol to the IRB within 7 days. If the research has been completed, or if the investigator does not plan to continue the research, the investigator is required to document as fully as possible the research that was conducted without IRB review. This documentation should include a description of the procedures that were followed, the number of subjects studied, and results of the study.

The department chair or the next higher level of administrative authority is notified of the above actions.

When an investigator wishes to continue the non-approved research, and a protocol has been received by the IRB, it is processed in the usual manner for exempt research.

Data collected prior to IRB approval will not be approved for publication or presentation purposes.

If the investigator fails to submit a protocol within the designated time, the IRB sends a written report, including a description of IRB actions, to the department chair or next higher level of administrative authority for appropriate action within 3 days. Failure of the

department chair to act or comply, is reported to the Chancellor with a recommendation for appropriate actions.

Non-exempt Research

The investigator is required to suspend the research at once. If the investigator plans to continue the research, he or she must submit a complete protocol to the IRB within 7 days. If the research has been completed, or if the investigator does not plan to continue the research, the investigator is required to document as fully as possible the research that was conducted without IRB review. This documentation should include a description of the procedures that were followed, the number of subjects studied, and results of the study and submitted to the IRB within seven days.

If there is a question, because of increased risk to subjects, as to whether the research should be suspended pending completion of protocol submission and approval, the Chair of the IRB counsels with the department chair and/or relevant experts. In case of failure to agree on suspension of the research, the determination of the Chair of the IRB will be final.

The department chair or the next higher level of administrative authority is notified of the above actions.

When an investigator wishes to continue the non-approved research and a protocol has been received by the IRB, it is processed in the usual manner for non-exempt research. The minutes of the appropriate meeting of the IRB will indicate that the protocol was submitted as a result of determination by the IRB that the investigator had been conducting human subject research without IRB approval.

If the investigator fails to submit a protocol within the designated time, the IRB sends a written report, including a description of IRB actions, to the department chair or next higher level of administrative authority for appropriate action within 3 days. Failure of the department chair to act or comply, is reported to the Chancellor with a recommendation for appropriate actions.

Data collected prior to IRB approval will not be approved for publication or presentation purposes.

Determination Of An Alleged Repeated Infraction Of Institutional Policy

The procedures outlined in "Determination of Alleged Infractions" above will apply for a repeated alleged infraction. If it is determined by the Chair of the IRB that a second or additional infraction has occurred, the IRB promptly notifies the Chancellor and the department chair or next higher administrative authority in writing, with the recommendation that the investigator's privilege to do research be suspended at once, that the funding agency be notified of the suspension, and that unused funds be

returned. It is also recommended that patients on therapeutic studies be changed to alternate therapy as soon as possible .