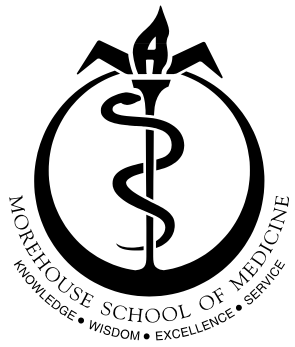

Morehouse School of Medicine

INSTITUTIONAL REVIEW BOARD

GUIDELINES, POLICIES & PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS

Institutional Review Board
Morehouse School of Medicine
720 Westview Drive, S.W.
Atlanta, Georgia 30310
404-752-1711
404-752-1973
404-752-1102

Revision of 2000 version: Completed March 2006

Morehouse School of Medicine
Human Research Subjects Protection Program

Declaration of Institutional Review Board Authority

The Institutional Review Board (IRB), a component of the Human Research Subjects Protection Program of Morehouse School of Medicine, constituted as required by federal regulations (45 CFR 46.101; 45 CFR 46.107; 21 CFR 56.101; 21 CFR 56.107) and well-respected ethical standards (The Belmont Report) to review and approve all research projects involving human subjects under the direction of the institution, shall have the authority to discharge its duties and responsibilities free from influence or coercion as declared by this document.

The IRB shall have the authority to approve, require modifications in, or disapprove all research activities under its jurisdiction (45 CFR 46.109(a); 21 CFR 56.109(a)). The institution shall not interfere with the deliberations or findings of the IRB. The institution reserves the authority to disapprove the conduct of human subjects research projects that have been approved by the IRB but cannot approve the conduct of human subjects research unless the IRB first confers approval (45 CFR 46.112; 21 CFR 56.112).

The IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with applicable federal, state or local regulations or laws, or the IRB's requirements as set forth in its policies (45 CFR 46.113, 21 CFR 56.113). The IRB shall have authority to suspend or terminate approval of research that has been associated with unexpected serious harm to human research subjects or others (45 C FR 46.113, 21 CFR 56.113). The IRB shall have authority to observe, or have a third party observe, the consent process and the research (45 CFR 46.109(e); 21 CFR 56.109(f)).

The operations and policies of the IRB shall follow all applicable requirements set forth in current federal, state and local law.

Responsibility for compliance with this declaration of authority and attendant policies and guidelines described herein shall be administered by the Vice President and Associate Dean for Sponsored Research Administration.

Institutional Approval Authority:

_____ _____
Signature Date
Vice President and Associate Dean for Sponsored Research Administration

_____ _____
Signature Date
Dean & Senior Vice President for Academic Affairs

INTRODUCTION

Governing Principles of the Human Research Subjects Protection Program at Morehouse School of Medicine (45 CFR 46.103(b)(1))

These guidelines and policies reflect the intention and obligation of Morehouse School of Medicine (MSM) to protect, to the fullest extent possible, the safety, autonomy, dignity and privacy of individuals who have volunteered to be human research subjects in studies conducted by Morehouse School of Medicine. The principles and requirements reflected herein are derived from ethical and legal authority expressed in the Belmont Report, the World Medical Association Declaration of Helsinki, the Nuremberg Code, Title 45 Code of Federal Regulations Part 46, and Title 21 Code of Federal Regulations Parts 50 and 56, as well as contemporary advisory opinions and standards issues by federal regulatory agencies charged with protection of human subjects in research.

Morehouse School of Medicine has provided a formal guarantee (Federal Wide Assurance 4535) to the Department of Health and Human Services (DHHS) that it will follow procedures that will assure the protection of all human subjects involved in research projects (45 CFR 46.103(a)). This guarantee applies to all human subjects research conducted by anyone on the premises of MSM and to research conducted elsewhere by faculty, students, staff, or other representatives of MSM in connection with their institutional responsibilities.

In order to comply with this assurance, MSM has established an institutional committee competent to review research projects that involve human subjects (45 CFR 46.103(b)(2); 21 CFR 56). Under the provisions of the DHHS Regulations for Protection of Human Subjects (45 CFR 46), as well as pertinent Food and Drug Administration Regulations (21 CFR 50; 21 CFR 56) this committee has been designated as the Institutional Review Board (IRB). The IRB consists of representatives from a variety of scientific and nonscientific disciplines as well as community members (45 CFR 46.107; 21 CFR 56.107). The primary function of the IRB is to assure protection of the rights and welfare of human research subjects. Investigators, however, carry primary responsibility for assuring that research protocols measure up to standards established by the federal regulations as well as institutional guidelines and policies. The IRB also serves to facilitate valuable human subject research as well as protect the investigator and the institution through a comprehensive review process.

Before a human subject research project is initiated it must first be reviewed and approved by the IRB and then conducted in full compliance with institutional guidelines and policies. The purpose of the IRB guidelines and policies is to provide MSM investigators with essential information and an educational resource that can be used in the preparation and submission of research proposals, including informed consent forms, for review by the IRB. The guidelines are also designed to provide information on the ethical and legal duties of investigators during the conduct of human subject research. These guidelines serve as an official governance document for human subject research at MSM.

Nothing in the IRB guidelines and policies/or the federal regulations governing human subjects research is intended to limit the authority of a physician investigator or any other health care personnel to provide

medical treatment or emergency medical care to the extent the individual is permitted to do so under applicable federal, state, or local law.

SECTION I

Institutional Review Board (IRB) Operations and Functions
45 CFR 46 Protection of Human Subjects
21 CFR 56 Institutional Review Boards

IRB RESEARCH PROTOCOL/PROPOSAL SUBMISSION AND REVIEW PROCESS REGULATORY COMPLIANCE

THE IRB APPLICATION/PROPOSAL SUBMISSION AND REVIEW PROCESS

A. INVESTIGATIONAL ACTIVITIES REQUIRING IRB REVIEW AND APPROVAL

Any systematic investigation (*research*, 45 CFR 46.102(d) or *clinical investigation*, 21 CFR 50.3(c); 21 CFR 56.102(c)) involving human subjects (45 CFR 46.102(f); 21 CFR 50.3(g); 21 CFR 56.102(e)), including research development, testing and evaluation, which is designed, in whole or in part, to develop or contribute to generalizable knowledge must receive IRB approval prior to initiation. This definition encompasses biomedical and sociological/behavioral research and may include investigations categorized as demonstration and service programs as well as some quality assurance programs. The term research includes clinical investigation (21 CFR 50.3(c)), and other descriptive terms such as clinical research, study, and clinical study (21 CFR 56.102(c)). This policy applies to human subjects research conducted by faculty, students, staff or others on the premises of Morehouse School of Medicine (MSM) as well as investigations conducted elsewhere by any representative of MSM in connection with their institutional responsibilities unless the investigation is conducted under a cooperative research agreement (45 CER 46.114; 21 CFR 56.114) or has otherwise been relegated to oversight by an IRB external to MSM. The level of review required depends upon the classification (Full-board, Expedited, Exempt) of the proposal as determined by the IRB using objective regulatory standards. Full-board review is the default required regulatory process (45 CFR 46.103; 21 CFR 56.103). Expedited review (45 CFR 46.110; 21 CFR 56.110) is permitted but not required. Exemptions (45 CFR 46.101(b); 21 CFR 56.104,105) are determined and documented by the IRB.

B. SUBMISSION OF APPLICATIONS FOR INITIAL REVIEW

Each investigator should carefully review the IRB submission requirements. Submission of incomplete applications or applications requiring significant modification may result in delay of the review and approval process. **The IRB and the Office of Research Development offer assistance in research proposal preview.** Investigators are urged to ask the IRB or Office for Research Development for a preview of their applications prior to submitting them for initial IRB review.

1. Required Materials for Review and Submission Process

The IRB accepts requests for review at any time; however, to facilitate timely and efficient review of research protocols, the IRB expects to receive the following, in typed format, **generally allowing a 30 day period prior to IRB meeting dates.** IRB meeting schedules as well as required forms may be found on the MSM IRB web site.

a. A complete IRB Initial Protocol Review Application
Send the application to the IRB office via e-mail and forward a copy with all pertinent signatures to the IRB office via mail or internal distribution.

b. Informed Consent/Parental Permission/Assent Form(s)
These documents must reflect IRB format, style and readability standards as described by the templates and discussed further in these guidelines. Each document should have a header or footer indicating the version (such as the date of application for review) of the document. Forward these documents via e-mail along with the application for review.

c. Detailed Research Protocol
The research protocol (grant application or other descriptive document) should include the following information in sufficient detail to convincingly show scientific merit and justification for undertaking the study.

Background
Objectives of the research project
Significance
Methodology
Clinical Information (where applicable)
Analysis of data
References
Investigational drug study registry (where applicable)

The protocol should demonstrate how the ethical principles of respect for persons, beneficence and social justice are taken into consideration.

d. Investigator's Brochure
For research requiring an Investigational New Drug Application (IND, 21 CFR 312) or Investigational Device Exemption (IDE, 21 CFR 812), please forward to the IRB office an electronic or hard copy of the Investigator's Brochure clearly indicating the assigned number pertaining to the application. Investigators are responsible to clarify with sponsors of drug studies or with the Food and Drug Administration whether an IND or IDE is required for the proposed research.

e. Research Subject Recruiting Materials and Methods
Forward to the IRB office, by e-mail or hard copy, copies of advertisements, brochures, or any other materials intended to be used in recruiting subjects in the proposed research. These materials must be reviewed and approved by the IRB before being distributed for recruitment of subjects.

Applications that are incomplete and/or not in compliance with IRB Guidelines will be returned to the investigator for appropriate revision prior to IRB acceptance for review. Investigators who have questions concerning their

proposal should contact the IRB administrator. The 30 day period allows the IRB to preview the application and provide feedback to investigators so that they may make changes prior to initial review.

2. Application Preview and Processing in the IRB Office.

Applications are previewed by the IRB administrator in consultation with the chair and or vice-chair of the IRB. Investigators are informed as soon as practicable as to the disposition of protocols qualifying for expedited review or those found to be exempt from IRB review according to current regulations. Investigators may contact the IRB office at any time to discuss the level of review required for contemplated research involving human subjects. Following IRB office preview, applications are recorded on an intake and tracking record and the research proposals are processed for review as described in C., below.

C. THE IRB APPLICATION REVIEW PROCESS AND PROCEDURES (45 CFR 46.103(b)(4); 21 CFR 56.108; 56.109)

The IRB review process reflects the various ethical principles and regulatory requirements that each investigator should consider during the design phase of their project. In order to approve a research project involving human subjects, the IRB must review and act upon credible information that demonstrates: 1) the prospective subject population is appropriate in terms of characteristics and number, 2) the recruitment of subjects is free of coercion, 3) the experimental design of the study is sound, 4) any risks associated with the research project are minimized to the greatest extent possible, 5) the potential benefits are maximized to the greatest extent possible, 6) the risks to the subject are outweighed or balanced by the potential benefits, 7) the level of subject compensation (if any) is fair and non-coercive, 8) the degree to which confidentiality is maintained is acceptable, 9) the method used to obtain informed consent is ethically and legally acceptable, and 10) the investigator has the appropriate qualifications, experience, facilities, and resources to conduct the research.

The IRB review process documents findings to ensure that the rights and welfare of the subjects are adequately protected and the protocol will be conducted in an ethical manner in full compliance with applicable policies and regulations. However, after IRB review has been completed and approval is obtained, it is possible that a research project may require additional levels of review. **IRB approval does not confer institutional approval to conduct the research study. As per 45 CFR 46.112 or 21 CFR 56.112, research that has been approved by the IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. Those officials cannot, however, approve any research project unless it is first approved by the IRB.**

1. General Review Criteria: The following criteria are taken into consideration for each protocol review:

a. Review of the Prospective Subject Population

The prospective subject population must be equitable (45 CFR 46.111(a)(3); 21 CFR 56.111(a)(3)) with respect to the nature and goals of the research. In addition, the investigator should be guided by the principles which lead to an equitable selection of subjects with regard to the potential risks and benefits of the research. The research application should reflect consideration of the burden of participation relative to social justice that would justify conducting the research. The IRB, therefore, will examine carefully the characteristics of the subject population. Factors such as the required number of subjects, age range, sex, ethnic background and health status will be considered.

Research involving vulnerable classes of subjects such as: critically ill, pregnant, fetuses, prisoners, children, elderly, mentally incompetent or cognitively impaired, or persons of low socioeconomic status must be clearly justified. In such cases, additional safeguards must be included to protect the rights and welfare of these subjects (45 CFR 46.111(b); 21 CFR 56.111(b)). Although research involving vulnerable persons as subjects is not prohibited by any regulations or ethical codes, justification for involving vulnerable persons in research generally becomes more difficult as the degree of risk and vulnerability increases and direct (research-related) benefits to individuals decrease.

Naturally, there are exceptions to the principle of "equitable selection of subjects". For instance, research involving the study of a disease to which one ethnic or racial group is primarily susceptible may well meet the requirement of social justice as the selection must obviously be narrowed.

b. Review of Method(s) of Subject Recruitment

The IRB will review the method of prospective subject identification and recruitment to assure it is ethically and legally acceptable. The IRB will review methods of recruitment to protect against potential coercion or undue influence. Information provided to subjects must not be misleading. Advertisements and recruitment materials should be informative and factual yet influence-neutral. Written recruiting/advertising material should be limited to: 1) a description of the study, clearly identified as research, 2) a brief description of eligibility, 3) incentives, without stating specific monetary amounts, and 4) study location and contact information. Advertisements and other methods used to recruit subjects are considered an extension of the recruitment and informed consent processes and, therefore, must be reviewed and approved by the IRB prior to use.

c. Review of Experimental Design

The IRB will review the experimental design in order to assure that potential risks to subjects are minimized and the potential benefits maximized by methods and procedures consistent with sound research design. The IRB will determine that the risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of knowledge that may be gained through the conduct of the research (45 CFR 46.111(a)(1)(2); 21 CFR 56.111(a)(1)(2)). The IRB has the authority to approve, require modification in (to secure approval), or disapprove a human subjects research protocol (45 CFR 46.109(a); 21 CFR 56.109(a)). When available, the IRB will examine internal and/or external scientific reviews. The scientific methods should provide justification for the ethical principles of respect for persons, beneficence, and justice, as well as an assessment of risks and benefits, and subject selection as described in The Belmont Report (Ethical Principles and Guidelines for the protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and behavioral Research, April 18, 1979, U.S. Government Printing Office: 1988).

The IRB accepts the need for certain types of behavioral and social science studies to employ strategies that include either deception and/or the withholding of information. Employment of such strategies must, however, be fully justified. In general, deception is not acceptable, if in the judgment of the IRB, the subject would have declined to participate had they been informed of the true purpose of the research. Studies which use deception and/or the withholding of information as part of their experimental design must include a post-study debriefing unless a waiver is granted by IRB.

The IRB recognizes the nature of certain research activities may seem controversial, e.g., genetic traits, social risks, racial/ethnic differences, etc. The IRB will apply objectivity in reviewing research involving moral or social impact dilemmas in that it will not speculate on the possible use or misuse of research findings to be within its purview as stated in 45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2). However, the IRB will scrutinize research protocols to ensure that the protection of privacy of personally identifiable information is reasonably addressed to maximize the maintenance of confidentiality and reduce risks associated with information collection and management.

In situations deemed appropriate by the IRB, individuals with competence in special areas of research under review will be consulted to assist in review where issues under review require expertise beyond or in addition to that available on the IRB. In such cases, the consultant reviewer(s) may present material for IRB deliberation but may not vote with the IRB (45 CFR 46.107(f); 21 CFR 56.107(f)).

d. Review of the Potential Risks

A risk is a potential harm (injury) associated with the research that a reasonable person, in what the investigator knows or should know to be the subject's position, would be likely to consider significant in deciding whether or not to participate in the research. The concept of risk includes any physical or emotional discomfort or burden, as well as inconvenience that a subject may experience as a result of the research procedures. Underlying the consideration of risk is the implicit moral guideline that all investigators have a duty not to harm their subjects and must minimize potential risk to the greatest extent possible.

The five major types of risks are: a) physical risk (e.g., pain, bruising and infection associated with venipuncture, adverse reactions to drugs, muscle soreness and pain as a consequence of exercise testing, angina induced by maximal exercise test); b) psychological risk (e.g., depression and confusion as a result of administration of drugs, feelings of guilt or anxiety precipitated by a sensitive survey, embarrassment, indignity); c) social risk (e.g., invasion of privacy, loss of community standing); d) legal risk (e.g., criminal prosecution or revocation of parole); and e) economic risk (e.g., loss of employment, loss of insurability or loss of potential monetary gain).

Both immediate and latent (delayed) risks of any procedure involving human subjects will be reviewed by the IRB. In addition, the estimated probability, severity, average duration, and reversibility of any potential harm will be considered according to available empirical data. Furthermore, since certain populations of vulnerable subjects may be at greater risk than others, the IRB will take into consideration the potential risk characterization of the subject. Pregnant women and their fetuses, for example, may be at greater risk in drug studies. Children, the elderly, prisoners, the mentally incompetent and various ethnic groups may incur an increased level of risk in certain kinds of research projects.

The degrees of risk may be classified as less than minimal, minimal, greater than minimal and significant. Federal regulations (45 CFR 46.102(i); 21 CFR 56.102(i) define minimal risk as “[t]he probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” The term "minimal risk" is used as a base or standard by which the risks associated with research are judged.

Currently, federal regulations governing human subjects research do not define risk categories other than minimal risk. However, 45 CFR 46, Subpart D – Additional DHHS Protections for Children Involved as Subjects in Research, reveals requirements that may be applied as well to other categories of vulnerable research populations such as those with diminished mental capacity. The considerations in research involving greater than minimal risk include: 45 CFR 46.405 – where the research

presents the prospect of **direct benefit** to individual subjects; 46.406 – where the research lacks direct benefits to research subjects but is likely to yield generalizable knowledge about the subjects' disorder or condition; and 46.407 - research that is not otherwise approvable but which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health and welfare of children, but only following approval by the Secretary of DHHS.

Further discussion of research-related risk may be found in other sections of these guidelines.

e. Review of Potential Benefits

A benefit is a valued or desired outcome. Benefits associated with participation in research can be classified generally as those that accrue to the subject directly (e.g., improvement of the subject's health status; acquisition by the subject of knowledge considered of value) and those that accrue to society (e.g., additions to the knowledge base). The IRB will review the anticipated benefits to both the subject and to others. In addition, the IRB will consider whether the benefits are maximized to the greatest extent possible through proper protocol design. Therefore, an underlying moral notion of "beneficence" should guide the investigator in the design and conduct of the research.

Financial or other forms of compensation or incentives are not considered benefits derived from research participation. Although the subject may consider financial compensation a desirable outcome, this fact will not be used in risk/benefit analysis.

f. Risk/Benefit Analysis

There are no strictly applied formulae applicable to arriving at a risk/benefit conclusion. The known risks and putative benefits are considered in light of the fact that research is intended to discover generalizable knowledge more so than to provide benefits to individuals. In this light, the greater the risks imposed by the research, the greater the need for ethical justification to conduct the research. In conducting its review of research, the IRB takes into consideration ways in which risks are minimized (45 CFR 46.111(a)(1); 21 CFR 56.111(a)(1)) as well as consideration of the reasonableness of risks in relation to anticipated benefits (45 CFR 46.111(a)(2); 21 CFR 56.111(a)(2)).

g. Review of Subject Compensation

The IRB will review the amount of compensation (monetary as well as other forms). In order to assure that it would not be considered coercive, or unduly influential, is distributed equitably, and reflects reasonableness in relation to subject involvement. Compensation should not appear to be purchasing participation and should be justified according to relative risks and burdens placed upon the subject.

h. Review of Confidentiality

The IRB will review the methods to be used to preserve confidentiality of information. If research data with subject identifiers will be made available to persons other than investigators, members of the research team, sponsors or federal agencies, the IRB will review the justification for sharing this data and determine acceptability of protective measures (45 CFR 46.111(a)(7); 21 CFR 56.111(a)(7)).

Under 45 CFR 164.508(b)(3)(i), the Morehouse School of medicine IRB does not require HIPAA authorizations for use or disclosure of protected health information to be combined with other regulatory requirements regarding informed consent to participate in research.

It is the policy of the IRB to request investigators to use stand-alone HIPAA authorizations permitting the use and disclosure of individually identifiable health information. The IRB need not approve stand-alone HIPAA authorizations.

The IRB defers to the responsibility of each covered entity under 45 CFR 160 and 164 to comply with use and disclosure requirements, including waivers and uses and disclosures for which authorization is not required as permitted under 45 CFR 164.512(i)(1)(i). A covered entity is basically the organization, unit or individual having custodianship of individually identifiable protected health information. (Reference: Guidance for Industry, IRB Review of Stand-Alone HIPAA Authorizations under FDA Regulations, October 21, 2003)

i. Review of Informed Consent

Although there are federal regulations requiring the subject or the subject's legally authorized representative to give consent prior to the subject's participation in research, the principal reason for informing subjects about the nature of experimentation is that they have a moral right to know what is to be done to them and what risks this entails before they give their consent. Human beings are considered autonomous and the requirement of informed consent is designed to uphold the ethical principle of "respect for persons" (The Belmont Report). The use of human subjects is a privilege -- a favor -- granted to the experimenter, rather than a right. An experiment is something that is done to the subject, and therefore differs from the usual medical practice where something is done solely for the patient.

In order for consent to be ethically and legally valid it must meet the requirements stated in Principle I of the Nuremberg Code and the informed consent section of the federal regulations (45 CFR 46.116; 21 CFR 50) which are based, in part, upon the Nuremberg Code. Principle I of the Nuremberg Code states, “The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of

force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision."

The legal documentation of informed consent is the consent form signed by both the subject and the investigator. The ethical and, indeed, legal validity of, consent is, however, dependent upon the process of informed consent which requires the investigator to engage in dialogue or negotiation with the prospective subject. The consent form, therefore, should be used by the investigator as an instrument to guide the negotiations with the prospective subject. The informed consent form must embody the elements of informed consent contained in the DHHS and/or other applicable federal, state or local laws or regulations. As presented in Section II of these guidelines and policies, the IRB will review both the consent form and the process of informed consent to ensure the preservation of autonomy of research subjects as well as to ensure adequate documentation of informed consent (45 CFR 46.111(a)(4),(5),(7),(b); 21 CFR 56.111(a)(4),(5),(7),(b)).

j. Review of Investigator Qualifications and Research Environment

The IRB will review investigator qualifications to assure the investigator has the appropriate qualifications and training to carry out the procedures described in the research. Investigators and each member of the research team must account for current training in human subjects research as required by the institution. In addition, the IRB may include in its review the adequacy of facilities, funds, equipment and personnel required to conduct the research.

k. Review of Research and Monitoring Requirements

The IRB will determine the interval of periodic/continuing project review. Projects are approved for a period of time in relation to the degree of risk not to exceed one year (45 CFR 46.109(e); 21 CFR 56.109(f)). Whether on initial or continuing review, the IRB considers the period of protocol approval on a case-by-case basis. Decisions as to whether a study should be reviewed more frequently than annually and at what interval(s) (45 CFR 46.103(b)(4)(ii); 21 CFR 56.108(a)(2)) are made in consideration of but not limited to the following criteria:

(1) the risk/benefit potential of the study along the following criteria:

(a) research determined to involve greater than minimal risk but is otherwise justifiable in relation to potential direct benefits to the research subjects.

(b) research determined to involve greater than minimal risk without direct benefits to research subjects but is otherwise justifiable as the research is likely to yield generalizable knowledge important to future applications.

(2) the complexity and scientific nature of the study (e.g., blinded, unblinded, degree of independent safety monitoring, the length of the study, as well as whether the study involves procedures or drugs/devices with which there is only limited experience in humans).

(3) adverse event reports or complaints of any nature regarding the study.

(4) whether subjects are particularly vulnerable or have compromised or diminished capacity to independently provide informed consent/assent to participate.

(5) the number of subjects to be managed at any given time in the study.

(6) safeguards described in the protocol or otherwise provided on site.

To ensure adequate protection of human subjects in research, the IRB may establish an appropriate monitoring procedure that may include observation of the consent process, observation of on-going research and review of research records (45 CFR 46.109(e); 21 CFR 56.109(f)).

On continuing review, the IRB shall, on its own discovery and authority or based upon external credible information, determine the extent to which verification from sources other than the investigator that no material changes have occurred since previous IRB review is required to ensure the integrity of the review process and protection of human subjects. In making such a determination, the IRB shall consider but not be limited to the following criteria:

- protocols determined to be of greater than minimal risk in which benefits to subjects are speculative or unlikely and involve vulnerable populations such as adults lacking capacity to consent for themselves or children considering age, maturity and the burdens imposed upon them to further the research

- protocols determined to be greater than minimal risk in which the investigator requires or relies upon expertise outside of the investigator's training and experience

- the IRB has had prior experience with regulatory or policy issues involving the investigator. Such experience includes reluctance or failure on the part of the investigator to comply with determinations of the IRB as well as evidence indicating changes having been made and implemented prior to IRB approval, except where such changes are determined to be for the immediate safety and/or well being of the subjects.

In verifying information to determine whether unapproved changes have occurred, from sources other than the investigator, the IRB shall make inquiries directed to parties knowledgeable about the specific research protocol. These parties may include but not necessarily be limited to:

- a resident research subject advocate
- the research sponsor or external review/advisory panel
- members of the research team
- research subjects

To ensure prompt reporting to the IRB of proposed changes in a research activity; and, to ensure that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate harm to subjects (45 CFR 46.103(b)(4)(iii); 21 CFR 56.108(a)(3),(4)), the IRB approval memorandum informs investigators as follows:

"Any advertisements, questionnaires or other written materials pertaining to human subjects must be reviewed and approved by the IRB before use in the project. Any changes made in either the protocol or the consent form must be brought to the attention of and approved by the IRB prior to implementation of such changes. If applicable, please bring this approval notice to the attention of the research administrator of any granting agency(ies) to which you have made application for funding. **Promptly notify the IRB of any changes in the protocol or consent process as well as any adverse events, or unanticipated problems to subjects or others as defined and required by current federal regulations and institutional policies.** This approval is issued with the understanding that you have read and agree to comply with all laws and regulations governing the conduct of this research involving human volunteers as well as the institutional **Guidelines and Policies for the Protection of Human Subjects.**"

In addition, the IRB may review investigator research files, and/or assign IRB members or a third party to observe the consent process or research activities (45 CFR 46.46.109(e), 21 CFR 56.109(f)).

l. Reporting of IRB Findings to Investigators and the Institution

Following reviews as discussed in sections below, the IRB documents its findings in review documentation records and sends written reports to investigators. Notifications of approval, disapproval, approval suspensions or terminations along with copies of all pertinent correspondence, where appropriate, are forwarded to the Vice President and Associate Dean for Sponsored Research Administration (45 CFR 46.109(d); 21 CFR 56.109(e)). For research investigations involving

exceptions to informed consent (21 CFR 50.24 Exception from informed consent requirements for emergency research), the IRB will promptly notify the investigator and the sponsor of the research in the event the IRB determines that it cannot approve the research because of failure to meet the criteria under section 50.24(a) or because of other relevant ethical concerns. The IRB will provide a written statement to the investigator documenting the reasons for its determination (21 CFR 56.109(e)). Presently, the institution does not conduct emergency research.

2. Initial Review Process

a. Expedited Review

If an investigation involves no more than minimal risk activities that qualify for expedited review status under current federal regulations and policies (e.g., 63 FR 60364-60367, November 9, 1998 – as may be amended in the future), the proposal may be reviewed by an expedited review procedure (45 CFR 46.110; 21 CFR 56.110). The IRB chair conducts expedited reviews or assigns expedited reviews to one or more other members of the IRB, taking into consideration the nature of the research and the expertise of the IRB member(s). Reviewers document findings on the expedited review documentation form. Within five to ten work days following receipt of the proposal, the investigator will be notified of the IRB's decision concerning the proposal. Reviewed proposals will be assigned to one of three categories:

(1) **Approved:** Notice of approval is sent to the investigator along with the approved informed consent document (if applicable) that is to be used for enrolling subjects. The investigator may begin the study.

(2) **Modifications/clarifications required:** The investigator will be notified in writing by way of a report of IRB protocol review as to the nature of the required modifications/clarifications. As soon as the investigator complies in writing with all requirements, a notice of approval will be issued and the investigator may begin the study.

(3) **Referred for full IRB review:** If the reviewer(s) raise(s) serious concerns, the proposal will be reviewed by the full IRB. The investigator will be notified in writing of this decision. Details of the questions and concerns raised will be reported to the investigator on the report of IRB protocol review form.

All research proposals approved using the expedited review procedure will be reported to the full IRB at the meeting following the date of approval. This is generally accomplished by publishing expedited reviews as items of business conducted between meetings on meeting agendas or as addenda to meeting minutes (45 CFR 46.110(c); 21 CFR 56.110(c)). All

IRB research protocol files are available for inspection and review by members of the IRB.

b. Full Board Review

Proposals that do not qualify for expedited review will be submitted to the full IRB. Following intake and preview, as described above, research protocols requiring full board review are assigned to a primary reviewer. The primary reviewer receives the entire file (including the Investigator's Brochure, when applicable). Reviewers document their findings and recommendations on the full board review documentation form. All IRB members receive a copy of the application for review and consent/assent documents. The primary reviewer presents findings at the convened meeting and makes a recommendation. The findings are discussed and all comments regarding changes to be made by the investigator and questions to be answered are recorded by the IRB administrator or other person assigned by the chair to record the minutes of the meeting. The primary reviewer, as well as any member of the IRB who wishes, submits a report of IRB protocol review form. Contents of the report form(s) are forwarded to the investigator for required action. In the event the primary reviewer is unable to attend the meeting, review findings and recommendations are forwarded to the IRB office and are presented to the IRB by the chair or a member designated by the chair. Within five to ten work days following the IRB meeting, the investigator will be notified of the IRB's decision concerning the proposal. Reviewed proposals will be assigned to one of four categories:

(1) **Approved:**
Notice of approval is sent to the investigator along with an approved informed consent document (if applicable) that is to be used for enrolling subjects. The investigator may begin the study.

(2) **Approved contingent upon specific minor modifications or clarifications:**
On occasion, the protocol, consent form or other pertinent document may contain minor errors of omission, syntax, and/or spelling. Examples of such errors would include but not necessarily be limited to: omission of a dosage unit, e.g., "mg," omission of a person on the research team, moving a sentence from one area to another, etc. The errors noted must be of a minor nature capable of recognition and correction by a person otherwise unfamiliar with the review process but familiar with word processing in general. The IRB office will make the necessary corrections to finalize approval or will contact the investigator to request corrections required to finalize approval. Following satisfaction of corrections to be made, a notice of approval will be issued and the investigator may begin the study.

(3) **Tabled:**
The IRB requires significant additional information and/or has a serious concern. Written findings are conveyed to the investigator

by way of the report of IRB protocol review form. The IRB administrator, chairman, vice chairman and/or an assigned member of the IRB may discuss the findings with the investigator to resolve issues raised in the review. Following resolution of issues and concerns raised, the proposal will be brought before the full IRB to complete the review at a subsequently convened meeting.

(4) **Disapproved:**
If a proposal is disapproved, the investigator has the right to respond to the IRB in person or in writing (45 CFR 46.109(d); 21 CFR 56.109(e)). When necessary, the IRB will seek consultation from qualified experts, other IRBs, the Office of Human Research Protections (OHRP) or the Food and Drug Administration (FDA). Every attempt will be made to resolve the identified problem(s). The IRB, however, retains final authority over whether or not a proposal can be approved; institutional officials may not approve research if it has not been first approved by the IRB (45 CFR 46.112; 21 CFR 56.112)).

c. Exempt Review

If a proposal is determined by the IRB to qualify for exempt status (45 CFR 46.101(b); 21 CFR56.104), the investigator will be notified within approximately five work days following receipt of the proposal. Exempt status is determined by review of the protocol by the IRB chair, administrator, vice chair, or an IRB member or members appointed by the IRB chair to review the proposal. Following the determination of exempt status, the investigator receives a memorandum of exempt research findings that describes how this conclusion was reached. The investigator is directed to notify the IRB of any changes negating this understanding.

3. Just-In-Time Review

The IRB will review human subjects research proposals submitted to the National Institutes of Health according to a change in policy announced in Notice OD-00-031, May 1, 2000. Accordingly, the IRB will act on this category of research following receipt of notice by the investigator that the proposal is likely to be funded (that is, the score received by the NIH review process is within a probable funding range). At that time, the IRB will commence the review process. The investigator must assure that "just-in-time" means sufficient time for the IRB to conduct its review. The IRB will not be influenced by pressure from investigators, the institution, or funding agencies to finalize its review process on short notice.

4. Institutionally-Supported Research

Investigator-initiated human subjects research protocols intended to be conducted as pilot or short-term studies supported through institutional funds must be documented with sufficient evidence of departmental and/or other institutional review and approval **prior to being submitted for IRB review.** Documentation

of departmental and/or other institutional review must be in writing and show sufficient detail as to considerations regarding scientific merit, adequate facilities and commitment of personnel. Research intended to be conducted in the Clinical Research Center must have the approval of the review body for the center as well as the director of the center. Research to be conducted at other sites must have the approval of the person authorized to commit facilities and/or personnel at those sites and may require filing or amending Federal-Wide Assurance documents and/or completion of unaffiliated investigator agreements.

5. Certification for Federal Funding or Agency Notice

The IRB will forward certification of IRB review and approval to the investigator, Office of Sponsored Research Administration. The investigator is responsible for forwarding notices of review and approval to sponsoring agencies. If a proposal is currently being reviewed by the IRB, the MSM research administration may inform sponsors that the research proposal is under review by the IRB; this will not express or imply that approval is a likely or certain outcome.

6. Continuing Review and Submission of Reports to the IRB

Whether through full board review; or, as allowed by expedited review, continuing IRB review of previously approved research is conducted at intervals appropriate to the degree of risk but not less than once per year (45 CFR 46.109(e); 21 CFR 56.108(a)1); 56.109(f)). Whether through an expedited process or by the full board, continuing review of research is conducted with the same degree of substantive and sifting scrutiny as applied to initial review. Non-exempt proposals are approved for a maximum period not to exceed one year. IRB members assigned to conduct continuing reviews receive the entire file to review including the informed consent document in current use as well as any changes having been approved, correspondence regarding the project and the investigator's continuing review report. Continuing reviews are conducted as thoroughly as initial reviews and members assigned to conduct continuing reviews complete a reviewer's report. Expedited continuing reviews are conducted by the chair or by one or more IRB members assigned by the chair. Due dates of continuing review reports are stated on approval notices to investigators. Generally, investigators will receive one additional notification regarding the due date of reports. Failure to timely submit a required report may result in termination of IRB approval and notification of such action to the institution and to the research sponsor. For projects requiring full-board continuing review, each member of the board receives a copy of the consent form currently in use and a copy of the investigator's continuing review report. For projects which are to be continued beyond the currently approved period, it is the responsibility of the principal investigator to timely submit continuing review reports. Continuing review reports are due upon the date stated in the current approval memorandum. If a continuation report has not been received by the IRB office before the approval period expiration date, the IRB notifies the investigator that all research activities must cease as the approval period has expired. Continuation reports received after approval period expiration are documented as delinquent and require the investigator to address the delay/gap in requesting continuation. Delinquencies may give rise to continued noncompliance with consequences following as described in section E, below. Upon timely receipt of

a continuing review report the IRB will review and approve, if appropriate, continuation of the project for a specified period. Irregularities in reports (e.g., changes or differences noted from protocol or deviations from approved consent) may delay review and re-approval. The IRB will contact investigators to clarify irregularities. If questions and issues remain to be addressed following explanation by the investigator, the IRB will delay the review and verify the information through sponsors or other parties who should be knowledgeable about the research in question. When a project is terminated or is otherwise completed, the investigator must immediately notify the IRB in writing and submit a closing report. The IRB will inform investigators of any further requirements regarding the project.

7. Reporting Proposed Changes in a Research Protocol or Changes in the Informed Consent Document or Informed Consent Process

Any proposed change in a protocol which affects human subjects must be reviewed and approved by the IRB prior to implementation, except where an immediate change is necessary to eliminate a hazard to the subjects (45 CFR 46.103(b)(4)(iii); 21 CFR 56.108(a)(3),(4)). Investigators must submit any requests for protocol changes on the Amendment to Previously Approved Research form as well as any changes to be made in the informed consent form, when applicable. Minor changes during the period for which approval is in force will be reviewed by an expedited review procedure to the extent permitted by current federal regulations and policies (45 CFR 46.110; 21 CFR 56.110). In reaching decisions regarding changes in previously approved research, the IRB will consider the following factors:

a. Protocol amendment:
Whether the amendment changes the risk/benefit ratio of the study.
Whether the amendment requires changes in the consent form.

b. Consent/Assent form/process amendment:
Reasons for the investigator's request to revise the consent form.
Whether the amendment requires notification to those who have already given consent via the previously approved version of the form.

c. Advertisement:
Appropriateness of content to ensure reflection of facts.
Whether the tone is over-reaching, i.e., inappropriately persuasive.
Whether a change in compensation anticipated to be paid to participants appropriately reflects considerations of risks and burdens imposed by the research.

d. Change in personnel:
In cases of addition or changes of personnel, whether the person filling the new position is qualified as to training, expertise and experience.
Whether changes in personnel need to be reflected in the informed consent document.

The IRB administrator, chair, vice chair or other IRB members designated by the IRB chair will determine and document whether the proposed change(s) in

previously approved research require full board review or may be processed by expedited review considering and justifying the expedited review category(ies) using the reference "Categories of Research That May be Reviewed by the Institutional Review Board (IRB) through an Expedited Review –Procedure" (45 CFR 46.110; 21 CFR 56.110) as published in 63 FR 60364-60367, November 9, 1998, currently in effect and as may be amended.

Minor changes to previously approved research (45 CFR 46.110; 21 CFR 56.110) will be reasonably determined in the context of the research and may include but not necessarily be limited to: clarifications of risks so long as any new risks do not elevate risk factors beyond greater than minimal, changes in personnel, modest changes in subject compensation for participation, changes in sequence of scheduling, addition or elimination of procedures that do not elevate risk factors beyond greater than minimal, changes that improve the risk/benefit ratio, and any changes that improve the understanding of informed consent.

If a change in protocol is relatively minor (e.g. change in the sequence of follow-up visits, change in personnel), it is not necessary to have the subject sign a revised consent form or an addendum to the consent form. If, however, the change is not minor (e.g., addition of an intervention not addressed in the original consent form or disclosure of a previously unidentified risk that elevates the risk level beyond greater than minimal) the investigator should have all new subjects sign a revised consent form and all currently enrolled subjects who are actively participating in the protocol sign an addendum to the previously approved consent form or sign the revised consent form.

D. REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

1. Interpretation of Federal Policy and Current Guidance

It is the intention of the IRB and the institution to diligently fulfill obligations to protect research subjects from harm. In fulfillment of reporting requirements set forth under 45 CFR 46.103(b)(5) and 21 CFR 56.108(b) directing institutions to assure prompt reporting of any unanticipated problems involving risks to human subjects or others, MSM principal investigators are required to report certain categories of adverse events as well as unanticipated problems that arise from the conduct of research under their supervision. In addition, principal investigators are often requested to submit to the IRB reports of adverse events from research sites other than MSM (off-site) that come to their attention. With respect to the latter, the IRB recognizes that investigators at MSM may receive off-site adverse event reports describing events that may have occurred weeks or months earlier. MSM investigators are to report off-site adverse events on the memorandum form: "Off-Site Adverse Event Reports," in a timely manner following the receipt of such reports, providing a brief description of the adverse events reported, whether or not principal investigators conclude with the findings and disposition of the report(s) and indicating their opinion as to whether the content of the report(s) should require changes to be made in the protocol or informed consent document or process. The IRB considers off-site reports to be for informational purposes only unless investigators inform the IRB that further action should be taken.

The IRB recognizes the difficulty in defining adverse events and unanticipated problems that would require reporting as contemplated in current regulations. Therefore, the IRB will consider any current guidance or agency directive addressing reporting of adverse events and unanticipated problems.

Not all adverse events are unanticipated problems and not all unanticipated problems in research are necessarily adverse events that elevate risks to subjects or others. The term "adverse event" is not found in current federal regulations controlling the conduct of human subjects research; however, it is the most commonly used expression intended to convey harm or injury in the context of human subjects research. The three most familiar federal regulations (45 CFR Part 46, and 21 CFR Parts 50 and 56) governing the conduct of human subjects research use the expression "unanticipated problems involving risks to subjects or *others*" (emphasis added). The regulations do not define "unanticipated problems" or "others" or what associated risks or severity of harm may give rise to unanticipated problems that would require "prompt" reporting to the IRB, appropriate institutional officials, and the department or agency head of HHS or the FDA.

There are, however, expressions in the regulations that may be reasonably interpreted as adverse events and/or unanticipated problems giving rise to risks to subjects or others. The terms described below are assumed to establish an interpretation of the term "unanticipated problem" requiring reporting as directed by the regulations. The common rule, 45 CFR 46, considers risks to include disclosure of private information that could reasonably place research subjects at risk of criminal or civil liability, or be damaging to financial standing, employability, or reputation (45 CFR 46.101(b)(2)(ii)). Research subjects must be informed of any foreseeable risks or discomforts (45 CFR 46.116(a)(2); 21 CFR 50.25(a)(2)). Although the FDA regulations do not contain this expression, it may apply as well to FDA research where investigators collect sensitive private information about subjects as part of or incidental to FDA-regulated research.

For purposes of fulfilling the requirement of reporting under the federal regulations cited in this section, the IRB considers the following to be examples of categories of incidences of adversities giving rise to unanticipated problems to subjects or others:

- harmful effects caused by drugs or devices
- complications from surgery
- harmful effects attributed to research procedures or lack of safeguards
- breach of confidentiality

The regulations do not define the nature or consequences, potential or experienced, of unanticipated problems that would be considered sufficiently severe as to require reporting. The IRB interprets the conditions described under 21 CFR 312.32 – IND Safety Reports – as indicia of severity of unanticipated problems that would require reporting under 45 CFR 46.103(b)(5) and 21 CFR 56.108(b):

- death
- life-threatening event

- hospitalization or prolonged hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- unanticipated adverse drug experience or the potential for such based upon errors in dosing, frequency of administration, formulation, dispensing, or product contamination

provided, however, that the examples and conditions described above are attributed to participation in research or are directly related to the research. In addition, the IRB will consider the consequences of breach of confidentiality as sufficiently severe as to require reporting based upon the degree to which subjects are exposed to, or actually experience, harm to their liberty or personal property interests as expressed under 45 CFR 46.101(b)(2)(ii), to include freedom from embarrassment as a valued personal property interest.

2. Reporting Unanticipated Problems Occurring at MSM

When a subject or other person involved in research in some way conducted at an MSM site suffers an adverse event, whether expected or not during the research, or experiences an unanticipated problem, the investigator must submit an "On-Site Adverse Event/Unanticipated Problem Report" to the IRB no later than 10 calendar days following the discovery of the event; except, in the case of the death of a subject or other person as a result of their association with the research, the IRB must receive notification within 48 hours of the time the investigator or any member of the research team learns of the subject's death. In general, an unanticipated adverse event or problem means an event that is not listed in the labeling for the test article (i.e., investigational drug or device) or was otherwise not reasonably foreseeable as a consequence of participating in the research. This term also includes a clinical event that may be symptomatically and pathophysiologically related to an event listed in the labeling but that differs from a possible anticipated event in quality or severity. An unanticipated adverse event or problem also means a clinical event that is previously unknown and/or is not expected on the basis of available clinical data or treatment experience. An unanticipated adverse event or problem includes harms or potential harms arising from breach of confidentiality.

Reports will be reviewed by the IRB staff, chair and/or vice chair. A timely determination will be made and the principal investigator will be notified of IRB recommendations. In reviewing adverse event reports, the IRB may seek consultation with appropriate experts as well as consider information provided by institutional or extramural data safety monitoring bodies. In reviewing reports, the IRB will determine whether the information provided justifies a continuation review period shorter than previously approved as well as whether the consent form content or process should be modified in light if the adverse event(s)/unanticipated problem(s) reported. The IRB will examine the report and confer with data safety monitoring boards or data safety committees, affiliated or external to MSM, when appropriate for advice and input. The IRB chair, vice chair or administrator in conference with the IRB chair or vice chair will determine whether the report warrants consideration and deliberation by the convened IRB; and, if so, when the IRB should convene to act on the report.

The IRB will forward on-site adverse event reports and its recommendations on such to the Office of Sponsored Research Administration within 5 working days following receipt of the report from the investigator except in the event of a reported death in which case the IRB will notify the Office of Sponsored Research Administration within one working day of having received the information from the investigator. The IRB will indicate whether the issues reported have been resolved, are anticipated to be resolved or remain uncertain as to resolution. The IRB will advise the Office of Sponsored Research Administration as to whether the reported incident(s) must be reported to sponsors and/or federal agencies as identified in I.E. below. The Office of Sponsored Research Administration will report to the sponsor and/or appropriate federal agency within 10 working days following notification from the IRB, except in the event of a reported death in which case the office of Sponsored Research Administration will report to the sponsor and appropriate federal agency within two working days following receipt of notification from the IRB.

If the IRB advises a report involving an unanticipated problem should be submitted to OHRP and/or the FDA, the Office of Sponsored Research Administration will include the following information in its report:

- the MSM location in which the adverse event/unanticipated problem occurred and the name of the person in charge of that location
- the title of the research project and/or grant proposal in which the problem occurred, including any identifying research project numbers assigned by the IRB or sponsor/granting agency
- the name of the principal investigator(s)
- a detailed description of the problem
- actions the institution is taking or plans to take to address the problem (e.g., stop the study, revise the protocol, suspend research activities, suspend subject enrollment, revise the informed consent document, inform enrolled subjects, increase the level of monitoring, etc.)

Nothing in this policy is meant to interfere with or otherwise alter investigators' reporting responsibilities as required otherwise by federal agencies or sponsors.

In compliance with the reporting requirements described in this section of the IRB guidelines and policies, the IRB referred to the following: OHPR "Guidance on reporting Incidents to OHRP" dated May 27, 2005 and OHRP "DRAFT Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or others" dated October 11, 2005.

E. REPORTING NONCOMPLIANCE WITH FEDERAL REGULATIONS, STATE LAWS AND AGENCY REGULATIONS, OR IRB REQUIREMENTS OR DETERMINATIONS

In addition to reporting unanticipated problems involving risks to human subjects or others as described in Section I. D., above, the institution is charged with the responsibility of reporting any instance of serious or continuing noncompliance with federal regulations governing the conduct of research in human subjects, or with IRB requirements or determinations, as well as any suspension or termination of IRB approval (45 CFR 46.103(b)(5)(i)(ii); 21 CFR

56.108(b)(1)(2)(3); 45 CFR 46.113; 21 CFR 56.113). The IRB must also consider laws and regulations of the State of Georgia as may be applicable in the context of human research subjects' protection. State laws that regulate professions as well as laws regulating administration and uses of drugs and controlled substances, e.g., as found under Title 43 – Professions and Businesses, Title 16 – Crimes and Offenses (includes the Georgia Controlled Substances Act and the Dangerous Drug Act), Title 24 – Evidence (includes confidentiality of research data), and Title 31 – Health (includes medical consent to treatment and surgery), are of particular relevance to human subjects research.

The IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with applicable federal, state or local regulations or laws, or the IRB's requirements as set forth in its policies (45 CFR 46.113, 21 CFR 56.113). The IRB shall have authority to suspend or terminate approval of research that has been associated with unexpected serious harm to human research subjects or others (45 C FR 46.113, 21 CFR 56.113). The IRB shall have authority to observe, or have a third party observe, the consent process and the research (45 CFR 46.109(e), 21 CFR 56.109(f)).

Any incident of non-compliance with federal policy or IRB guidelines should be reported in a timely manner (refer to 2.a., below) to the IRB. Non-compliance with IRB requirements is a violation of MSM's Federal-Wide Assurance and the federal regulations for the protection of human subjects. Non-compliance may result in suspension or termination of IRB approval. All incidents of non-compliance reported or otherwise coming to the attention of the IRB will be brought also to the attention of appropriate department/unit heads, the Office of Sponsored Research Administration.

1. Interpretation of Federal Policy on Noncompliance and IRB Actions

Noncompliance is reasonably interpreted to mean willful, negligent, or inadvertent disregard of requirements expressed in guidelines, regulations and policies. Continuing noncompliance results when ongoing acts or omissions continue beyond requests to cease activities or, intermittently, when such acts or omissions result in a pattern of delays in responding or submitting reports as required by guidelines, regulations, and policies. Serious noncompliance is of a nature having important, significant or dangerous possible consequences that call into question the integrity of the research, the safety and welfare of human subjects, and/or the reputation of the institution.

Examples of noncompliance applicable to guidelines, regulations and policies herein expressed include but are not necessarily limited to the following:

- Failure to obtain IRB approval to conduct human subjects research
- Failure to conduct an adequate informed consent process
- Failure to comply with IRB directives
- Failure to adequately supervise research
- Failure to follow approved research protocols
- Failure to follow established research policies
- Failure to follow reporting requirements
- Failure to seek IRB approval prior to initiating changes in an approved

study

- Failure to comply with training and educational requirements
- Failure to comply with laws and regulations governing businesses, licensing, and professions in the context of human subjects research
- Failure on the part of the IRB to conduct appropriate level or adequate documentation of review of research or in its discharge of other responsibilities with which it is charged by regulation or institutional policies and guidelines.

Administrative hold on research activities is a directive issued by the IRB in situations where suspension or withdrawal of IRB approval to conduct human subjects research is not clearly warranted. The IRB will notify investigators and appropriate institutional officials of the reasons for placing a study on administrative hold in a timely manner following a review of facts and documentation of events leading to this decision. The decision is made by the IRB chair or administrator of the IRB. The IRB considers this action as temporary in order to complete a more thorough investigation into matters pertaining to this decision. Following its review in discharging due diligence, the IRB will present investigators and appropriate institutional officials with its plan to address and correct issues identified by its review. An administrative hold may include restrictions on recruitment and conducting further research on subjects until resolution has been reached or further action is taken by the IRB. If warranted by the nature of incidents resulting in issuing an administrative hold, the IRB chair may decide to present the information to the IRB membership seeking advice as to whether issues warrant further action by the assembled IRB. An administrative hold on research may result in resolution lifting the hold, suspension of IRB approval, or withdrawal of IRB approval. An administrative hold is regarded as permissible in the judgment of the IRB chair or administrator but is not necessarily required as the first step in addressing issues of suspected noncompliance. In the event the administrative hold results in either suspension or withdrawal of IRB approval, the course of action described in section E.3. below applies.

Suspension of IRB approval is an order from the IRB to cease all research activities, except as required for subject well-being and safety, in a specified protocol. No new recruitment will transpire during a period of suspension. A suspension is issued to allow investigators and the IRB to correct the incidence of noncompliance in a timely manner. In issuing a suspension of approved research, the IRB will determine whether there are changes in the risk/benefit ratio that would require additional protections for subjects. The IRB will request and consider a report from the investigator addressing the issue of noncompliance and presenting a plan to prevent further instances of noncompliance.

Withdrawal of IRB approval to conduct human subjects research is an order from the IRB that terminates all activities involved in a specified protocol, except as required to prevent harm and preserve well-being of enrolled subjects. The intent of withdrawal of IRB approval is a permanent discontinuation of research activities in the specified study. Withdrawal of IRB approval will be issued in cases where an intermediate course of action, e.g., suspension, would be an inappropriate remedy to ensure the safety and well-being of subjects given the gravity of noncompliance.

2. How Reports or Notices of Noncompliance May Come to the Attention of the IRB

a. Investigator-initiated reports: It is the responsibility of the investigator or any research team member to report any serious or continuing noncompliance, as described but not necessarily limited to examples cited above, to the IRB within 5 calendar days following discovery or otherwise becoming aware of such noncompliance. The report should indicate the nature of noncompliance, the identity of other parties, e.g., sponsors, agencies, administrative units, having knowledge of the incidence(s) of noncompliance, and copies of any communications or summaries of conversations regarding the noncompliance involving parties other than the IRB. The individual submitting the report should detail any actions taken to correct the issues of noncompliance and present a plan of action to prevent further incidences of noncompliance. The report should state to what extent subjects may have experienced harm as the result of noncompliance and identify any steps taken to minimize current harm and prevent future harm. The report should indicate to what extent subjects were made aware of the acts or omissions resulting in noncompliance.

b. Other sources of reports: The IRB may learn of noncompliance through reviews or inspections of research activities or through other parties such as research subject advocates, research subjects, subjects' family members or care-givers, sponsors, regulatory agencies or administrative units or other personnel. In cases where notification of noncompliance is brought to the attention of the IRB through a process other than by investigators, the IRB will present the information to the investigator, protecting anonymity where the IRB deems appropriate to do so, to allow the investigator a reasonable opportunity to provide feedback to the IRB.

3. Actions to be Taken Following IRB Review of Noncompliance and Institutional Reporting Requirements

a. Regardless of whether the IRB has issued an administrative hold on research, in cases where the IRB determines it must issue an order for suspension or withdrawal of approval to conduct research, the IRB's first course of action will be to ensure the safety and welfare of human subjects that may have been affected by or may be potentially affected by the acts or omissions of noncompliance. The IRB will conduct a review and attempt to resolve the issues of noncompliance in a thorough and timely manner but will not in any case accelerate its actions because of inconveniences and delays in conducting research activities. The IRB office will notify the IRB membership of incidences of unresolved noncompliance. The IRB chair and/or members of the IRB may be appointed to conduct an investigation on the matter of noncompliance. Depending on the gravity of the incidence under investigation or in cases failing to reach a timely resolution, the matter will be presented at a convened meeting of the IRB.

Within 2 working days of issuing an order for suspension or withdrawal of IRB approval, the IRB will forward a preliminary written report to the investigator describing the reasons for issuing a suspension or withdrawal of approval. A copy of the report will be forwarded to the Office of Sponsored Research Administration. The investigator must respond to the IRB's determination within 5 working days of the date of suspension or withdrawal of IRB approval. The investigator must describe a course of action to correct noncompliance.

Following analysis of the investigator's response and proposed course of action, within 2 additional working days, the IRB will determine whether the matter has been resolved and reinstate approval or whether the suspension or withdrawal of approval should remain in effect. In cases where the IRB determines that matters pertaining to 45 CFR 46.103; 21 CFR 56.108 have not resolved and the IRB continues the order for suspension or withdrawal of approval, the IRB will inform appropriate institutional officials to report the action taken to the agencies identified in I.E.3.b., below, as may be applicable to the case in question.

b. The IRB considers the person responsible for the Office of Sponsored Research Administration to be the appropriate institutional official to be notified and responsible for reporting to federal agencies as required by regulations. Reports sent by the Office of Sponsored Administration should include the following information:

For serious or continuing noncompliance:

- the MSM location, unit, department, etc., in which the research is conducted and the name of the person in charge of that location
- the title of the research project and/or grant proposal in which the noncompliance occurred, including any identifying research project numbers assigned by the IRB or sponsor/granting agency
- the name of the principal investigator(s)
- a detailed description of the noncompliance
- actions the institution is taking or plans to take to address the noncompliance (e.g., stop the study, require further education on humans subjects research and applicable regulations/guidelines, suspend research activities, suspend the investigator, suspend subject enrollment until noncompliance is addressed, conduct random audits of the study, etc.)

For suspension or termination of studies:

- the MSM location, unit, department, etc., in which the research is conducted and the name of the person in charge of that location
- the title of the research project and/or grant proposal suspended or terminated via suspension or withdrawal of IRB approval or through administrative authority, including any identifying

research project numbers assigned by the IRB or sponsor/granting agency
- the name of the principal investigator(s)
- a detailed description of the reason for the suspension or termination
- actions the institution is taking or plans to take to address the suspension or termination (e.g., requiring the investigator and or research staff to undergo further education and training in the conduct of human subjects research and applicable regulations and guidelines, other stipulations required before the suspension or termination is lifted, conditions of monitoring the investigator and research, etc.)

c. Based on IRB determinations as described in I.D. and I.E. of these IRB guidelines and policies, the appropriate institutional official will report any instance of serious or continuing noncompliance with federal regulations governing the conduct of research in human subjects, or with IRB requirements or determinations, as well as any suspension or termination of IRB approval (45 CFR 46.103(b)(5)(i)(ii); 21 CFR 56.108(b)(1)(2)(3); 45 CFR 46.113; 21 CFR 56.113) to:

(1) The U.S. Food and Drug Administration:

(a) For cases involving drug products:
Division of Scientific Investigations (HFD-45)
Office of Medical Policy
Center for Drug Evaluation Research
7520 Standish Place
Rockville, MD 20855
Phone: 301-594-0020
Fax: 301-594-1204

(b) For cases involving biologic products:
Bioresearch Monitoring Branch (HFM-664)
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
for Biologics Evaluation and Research/FDA
1401 Rockville Pike, Room 400S
Rockville, MD 20852-1338
Phone: 301-827-6347
Fax: 301-827-6748

(c) For cases involving medical devises:
Division of Bioresearch Monitoring (HFZ-310)
Office of Compliance
Center for Device and Radiological Health (CDRH)
2094 Gaither Road
Rockville, MD 20850
Phone: 301-594-4718
Fax: 301-827-6748

(2) The Department of Health and Human Services
Office for Human Research Protections
Compliance Oversight
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Phone: 301-435-8072
Fax: 301-402-2071

F. RECORD KEEPING

The IRB maintains documentation of activities and records in compliance with 45 CFR 46.115 and 21 CFR 56.115. Review documentation, research-related records and correspondence are generally maintained in individual project files within the IRB office. IRB meeting agendas and minutes are maintained in binder files in the IRB office. Contents of minutes reflect sufficient detail and information described under 45 CFR 46.115(a)(2) and 21 CFR 56.115(a)(2); a current list of IRB members (45 CFR 46.115(a)(5); 21 CFR 56.115(a)(5)) is attached to each set of approved IRB minutes. The IRB office maintains written procedures as required under 45 CFR 46.115(a)(6) and 21 CFR 56.115(a)(6). Records are retained and are accessible as required under 45 CFR 46.115(b) and 21 CFR 56.115(b). The IRB may choose to maintain and store original or duplicate documentation, records and correspondence in electronic file formats in a manner consistent with regulatory requirements.

Exempt status research files are maintained in the IRB office for a period of one year and are then discarded.

G. CATEGORIES OF RESEARCH REQUIRING ADDITIONAL PROTECTIONS AND CONSIDERATIONS – "Vulnerable Subjects"

1. Pregnant Women, Human Fetuses and Neonates Involved in Research

These categories of human subjects require additional protections as described under 45 CFR 46 Subpart B – as amended and effective December 13, 2001 (FR, 11/13/01, Vol. 66, No. 219, Rules and regulations, Pages 56775 – 56780). The IRB will review all research involving these categories of vulnerable subjects with heightened scrutiny to determine whether sufficient safeguards are in place to maximize the well-being and safety of the subjects as well as to ensure all applicable sections of Subpart A have been met. In reviewing research involving pregnant women or fetuses, the IRB will review and document its findings as to each applicable criterion as described under 45 CFR 46.204(a) – (j). In reviewing research involving neonates, the IRB will review and document its findings as to each applicable criterion as described under 45 CFR 46.205(a) – (d). In reviewing research involving, after delivery, the placenta, the dead fetus or fetal material, the IRB will review and document its findings as to each criterion described under 45 CFR 46.206(a)(b). In reaching conclusions in its review process, the IRB will take into consideration risks imposed by the research, any direct benefit to the women, fetuses or neonates anticipated to derive from the research as well as justifications in conducting research in which no benefit to

subjects is anticipated. Reviews involving these categories of vulnerable subjects include research of any nature unless the research is determined by the IRB to be exempt under the provisions of 45 CFR 46.101(b).

Food and Drug Administration Categorization of Drug Risks to Fetus

Category A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
Category B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Category C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. **Drugs should be given only if the potential benefit justifies the potential risk to the fetus.**
Category D	**There is positive evidence of human fetal risk**, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X	Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and **the risk of the use of the drug in pregnant women clearly outweighs any possible benefit**. The drug is contraindicated in women who are or may become pregnant

In the event pregnancy is discovered at some time subsequent to enrollment in research, the investigator must send a report to the IRB within a reasonable time of such notice having come to the attention of the investigator. The report will explain how the research will be brought under Subpart B compliance as to pregnant subjects. Such report will detail why it is in the best interest of pregnant subjects to continue in the research and to what extent the informed consent process must be changed. If the investigator determines that it is in the best interest of pregnant subjects not to continue in the research or pregnant research subjects decide autonomously to withdraw from the study, the investigator must describe a procedure addressing the safe, orderly, withdrawal of pregnant subjects from the research activity and any follow-up intended to take place after a subject's participation terminates.

2. Prisoners as Research Subjects

This category of human subjects research requires additional protections as described under 45 CFR 46 Subpart C as well as the Office for Human Research protections "OHRP Guidance on the Involvement of Prisoners in Research" (May 23, 2003 revised September 3, 2004, or as may be amended subsequently). The

IRB will review research involving this category of vulnerable subjects in compliance with additional safeguard requirements to include: composition of the IRB as described under 45 CFR 46.304 and review and documentation of additional IRB duties as described under 45 CFR 46.305 considering permissible categories of research described under 45 CFR 46.306. In its review and documentation process for research involving epidemiological studies on prisoners, the IRB will consider waiver of 45 CFR 46.305(a)(1)and(2) as described in the FR Vol. 68, No. 119, 6/20/03, 36929 – 36931, effective June 20, 2003. For purposes of reviewing research involving prisoners, the IRB considers a person who is incarcerated or under detention of police-power authority to be a prisoner. A person who is on parole or on probation is not considered to be a prisoner subject to the requirements of this subpart. In determining the risks to subjects in this category, the IRB will apply the definition of minimal risk as described in 45 CFR 46.303(d).

In the event a subject becomes a prisoner at some time subsequent to enrollment in research, the investigator must send a report to the IRB, within a reasonable time of such notice having come to the attention of the investigator. The report must include a plan describing how the research will be brought under Subpart C compliance as to prisoner research subjects. The plan will detail why it is in the best interest of prisoner subjects to continue in the research and to what extent the informed consent process must be changed. The plan must detail how prison authorities will allow access to the prisoners in a manner that preserves the best interest of the prisoners as well as the context of the research. If the investigator determines that it is in the best interest of prisoner subjects not to continue in the research or prisoner research subjects decide autonomously to withdraw from the study, the investigator must describe a procedure addressing the safe, orderly, withdrawal of prisoner subjects from the research activity and any follow-up intended to take place after a subject's participation terminates.

3. Children Involved as Subjects in Research

This category of human subjects research requires additional protections as described under 45 CR 46 Subpart D and 20 CFR 50 Subpart D, as well as "OHRP Guidance on Protections for Children as Research Subjects" (August 31, 2005; or as may be amended subsequently); "OHRP Secretary's Advisory Committee on Human Research Protections – Appendix B (pertaining to research involving children under 45 CFR 46.404; 405, and 406), November 25, 2005. The IRB will review research involving this category of subjects in compliance with additional safeguards and protections taking into consideration the exception of exemption at 45 CFR 46.101(b)(2) as described under §46.401(b). The IRB will review and document its findings in satisfaction of the conditions of all applicable sections expressed in 45 CFR 46.403 and 21 CFR 50.50 and approve only those investigations that satisfy the criteria described in §§46.404, 46.405, 46.406 and 46.407; and, as applicable to §§50.51, 50.52, 50.53 and 50.54. Parental or guardian permission and solicitation of assent by children to participate in research will be determined by the IRB in accordance with 45 CFR 46.408 and 21 CFR 50.55, as applicable, including exceptions, additions and provisions for waiver as described under 45 CFR 46.401(c), where applicable to the nature of research under review. Details of informed consent, parental or

guardian permission and assent processes are discussed further under Section II of these guidelines and policies.

For the purpose of IRB review of research in this category of subjects, the terms minor and child will be considered to be synonymous and the legal status of minor or child will be identified according to current federal and state law. Generally, in the State of Georgia, a person under 18 years of age is considered a minor for transactions involving health care. The State of Georgia does not have an emancipated minors act.

4. Other Categories of Potentially Vulnerable Persons

The IRB considers the following factors in determining whether additional protections may be required:

- Employees
- Students at any level of education
- Economic status
- Education level
- Physical or medical disability/compromise
- Mental capacity/compromise:
  - Cognitive impairment/mental disease
  - Influence of medication/addiction
- Sensory impairment/sight/hearing
- Relationship between investigator and subject
- Cultural/ethnic origin and customs
- Social stigmatization
- Colloquial issues

SECTION II

Informed Consent

45 CFR 46 Protection of Human Subjects
21 CFR 50 Protection of Human Subjects

REQUIRED ELEMENTS AND PROCESS OF INFORMED CONSENT
and
ASSENT OF MINORS

A. INFORMED CONSENT REQUIREMENTS/ELEMENTS

The purpose of this section is to assist the investigator by providing guidance on how to construct and obtain valid informed consent, assent where appropriate in the case of minors, from prospective research subjects. The IRB informed consent requirements are based on current DHHS and FDA regulations (45 CFR 46.116, 46.117 and as applied in subsequent sections; 21 CFR 50 Subpart B), Principle I of the Nuremberg Code and applicable principles as enumerated in the World Medical Association Declaration of Helsinki. To this end, any member of the IRB may be contacted for advice on writing informed consent documents.

1. General Requirements of Informed Consent

Under the provisions of 45 CFR 46.116 and 21 CFR 50.20, unless provided elsewhere in these respective federal regulations and policies, an investigator may not involve a human subject in research without first having obtained the legally effective informed consent of the subject or the subject's legally authorized representative. As to exceptions regarding informed consent in either the DHHS or the FDA regulations and policies, Morehouse School of Medicine does not engage in the conduct of emergency research. In the absence of a judicially appointed guardianship or evidence of a legally effective advanced directive/power of attorney, the IRB shall consider the State of Georgia law regarding consent to medical treatment as described under OCGA 31-9-2 to apply as well to research and to fulfill the definition of legally authorized representative as contemplated under 45 CFR 46 and 21 CRF 50.

2. Basic Elements of Informed Consent

a. With applicable exceptions as may be allowed by regulation and determined to be appropriate by the IRB, each of the following must be contained in the informed consent document:

(1) a statement that the study involves research, explaining the purpose of the research, the anticipated duration of the subject's participation (including any intentions to conduct follow-up activities), a description of the procedures to be followed, and clear identification of any procedures that are experimental.

(2) a description of any reasonably foreseeable risks, discomforts and/or inconveniences to the subject. This description should include, to the best of the investigator's knowledge, experience and training, reasonable levels of anticipated frequency known to be associated with such risks. The anticipated frequency of risk occurrence may be derived from published compendia of medical information.

(3) a description of any benefits to the subject or to others which may reasonably be expected from the research. Such benefits must be related to the purpose of the research and not merely coincidental to participation. Stipends or other forms of gratuity are not

considered research-related benefits. As contemplated by this element, "others" may be interpreted as persons similarly situated that may benefit from the research at some time in the future.

(4) a disclosure of alternative appropriate procedures or courses of treatment, if any, that might be advantageous to the subject. Included in this element would be a statement that the subject may receive the same treatment, procedure, benefit, etc., regardless of participation in the research, if in fact that is true. For example, this is often the case in drug comparison studies where the drugs are approved for the use intended in the research design.

(5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. This statement should include the possibility that sponsors, the IRB and federal agencies, where applicable, may inspect research records (21 CFR 50.25(a)(5); 56.115(b); 45 CFR 46.115(b)).

(6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained. The suggested statement in the IRB's informed consent form template is provided as a guide to meet the requirements of this element. Any alterations in wording this element should avoid express or implied exculpatory statements, further described in B. below.

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

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

b. Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject: (Note as to the elements enumerated below: the IRB believes this information should be included as a matter of principle and has included these elements in the informed consent document template.)

(1) a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently foreseeable. The statement need not be an exhaustive list of every risk possibility known but should reflect the most common risks and their relative frequencies (probabilities) of occurrence. As to risks involved with

administration of drugs, the frequencies of occurrence may be expressed as a percentage or other meaningful description as may be published in medical or prescribing literature. Description of risks should not be understated. The most commonly reported risks should be described as well as risks that rarely occur but may pose serious threats to the subject should they occur. A description of risk factors should include those risks which may be expressed as:

- Physical harms to the subject or others.
- Disclosure of information that could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- Disclosure of information that may damage subjects' relationships to others such as family members or spouses.
- Disclosure of information that may have a wide-spread negative social impact on a particular group or race/ethnicity.

(2) anticipated circumstances under which the subject's participation may be terminated by the investigator without the subject's consent. This determination may be based upon the subject's unwillingness to follow procedures or may be based on some event indicating it would be in the best interest of the subject not to continue participation in the research. This may also be the case where a sponsor or an investigator decides the research should not proceed. In any event, when a decision to terminate participation is reached, the subject(s) must be informed of the basis of the decision to terminate their participation as well as given information that may be pertinent to their well being.

(3) any additional costs to the subject that may result from their participation in the research.

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

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

(6) the approximate number of subjects involved in the study. This element should be stated as to nationally, or globally, where appropriate as well as locally.

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

(1) the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (1) 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 the methods or levels of payment for benefits or services under those programs; and

(2) the research could not practically be carried out without the waiver or alteration. (Note: Investigators must describe in detail and justify a waiver or alteration as considered in this section. Mere inconvenience to contact subjects is not an appropriate justification to allow a finding for waiver or alteration as contemplated The IRB has the authority to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent as set forth above, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(a) the research involves no more than minimal risk to the subjects. (Note: minimal risk as defined by 45 CFR 46.102(i); 46.303(d); 21CFR 50.3(k); and, as described in "Categories of Research That May Be reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure" *Research Categories* (1) – (9), 63 FR 60364-60367, November 9, 1998.)

(b) the waiver or alteration will not adversely affect the rights and welfare of the subjects. Considered in this element are rights and welfare including but not limited to privacy, employment, insurability, reputation, standing in the community, as well as potential exposure to civil or criminal liability.

(c) the research could not practically be carried out without the waiver or alteration. (Note: refer to II.A.2.(c)(2) above.)

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

In general, although the IRB provides an informed consent form template that seeks to standardize elements of informed consent, the IRB allows investigators considerable latitude in the design and content of the consent form to meet particular research needs. As a matter of ethical principal, The IRB may suggest a consent document be used in research activities determined to be exempt from the requirements of federal regulations.

B. THE PROCESS AND DOCUMENTATION OF INFORMED CONSENT

1. Informed Consent Process Requirements and Considerations

The ethical principle of informed consent is respect for personal autonomy. The IRB recognizes that the complexity of both the consent form and the process of informed consent will vary according to the nature of the research and the level of associated risk. In addition, the process of informed consent must consider a variety of subject-related factors that may impact and influence the informed consent process. The federal regulations (45 CFR 46.116; 21 CRR 50.20) clearly delineate requirements in the process of informed consent:

- An investigator may not involve a human subject in research unless the investigator has first obtained the legally effective informed consent of the subject or the subject' legally authorized representative. "Involve" in research is interpreted to mean any aspect of the research including any qualifying steps or tests to determine whether the subject meets criteria required to participate.

- An investigator shall seek consent of a subject only under circumstances that provide the subject or the subject's representative sufficient opportunity to consider whether or not to participate. "Sufficient opportunity" is interpreted to mean a reasonable time before subjects make a decision whether or not to participate. The more complex the study, the more time should be allowed for this decision-making process.

- The consent process should minimize the possibility of coercion or undue influence. Compensation for participation should not be made to appear as though participation is being purchased. Compensation should reflect the complexity and associated risks of subject involvement. The consent process must not be designed to influence a decision to participate; this decision must be of the subject's free will.

- Information given to the subject or the subject's representative must Be in a language understandable to the subject or the representative. This requirement is interpreted to mean in a manner that the subject will be capable of interpreting. The reading level of the informed consent document should be considered and tailored to meet the general subject population anticipated to enroll. The IRB generally requests readability tests to meet criteria based upon 6^{th} to 9^{th} grade reading levels as generally ascertainable in word processing programs or through the assistance of language expertise. If informed consent documents are to be presented in a language other than English, the IRB shall seek translating expertise in assessing readability and understandability.

- No informed consent process, whether written or oral, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or

releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

The purpose of the written consent form is to assist the process of providing full disclosure of relevant information sufficient to enable the subject to understand the nature and scope of the research. In the process of informed consent, the investigator has a legal and an ethical obligation to ensure that the prospective subject has sufficient knowledge and comprehension of the elements of informed consent. This means the prospective subject must be able to make an understanding and enlightened decision to participate in research. In the research context, the subject's participation benefits the investigator and science regardless of the outcome. Obtaining valid informed consent, whether written or oral, should be accomplished by taking into consideration the educational level and other personal factors that may influence a subject's understanding and willingness to participate in research. A consent form, however, does not by itself constitute informed consent and the duty of care owed to the subject is not diminished by the subject signing the form that implies assumption of risks. During the process of informed consent each element of consent should be carefully, patiently, and simply explained to the prospective subject. In addition, the investigator should periodically assess the prospective subject's comprehension by asking appropriate questions. In some cases, the consent process should be extended over several days and involve other individuals such as the prospective subject's spouse, or other family members. It must, however, be remembered that the investigator bears full and ultimate responsibility for obtaining valid informed consent from the subject. To this end, it is extremely important that this responsibility is discharged by the investigator, personally, or by an agent of the investigator having equal authority and knowledge to conduct the research and answer questions raised by potential subjects. The IRB encourages investigators and research personnel to periodically ask subjects if they have any questions about participation or the consent process.

As the process of informed consent is the most important aspect in obtaining legally valid consent, it is advised that the investigator, or other persons qualified to obtain consent, make notes on the research record documenting discussions with the subject during the consent process.

2. Documentation of Informed Consent

a. General Requirements

As required by 45 CFR 46.117(a) and 21 CFR 50.27(a); unless the IRB finds and documents exceptions noted below, consent must be documented by the use of a written form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative. Although not required by regulation, the IRB requires the signature and date of the person responsible for obtaining written informed consent. Except in circumstances described below, a witness signature is not required by regulation. However, sponsors, the IRB, or researchers may request witness documentation of informed consent when advisable. The IRB considers a form approved by the IRB to be identified by a header describing the approval process and approval period during which the form may be used. The IRB considers the header to represent a "stamped" version of the consent form.

b. Consent Form Format

Except as provided in II.B.2.c., below, the consent form may be either:

(1) A written consent document that embodies the elements of informed consent described under II.A.1. and II.A.2., above. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator or person responsible for obtaining informed consent shall give either the subject or the representative adequate opportunity to read the consent form before it is signed (45 CFR 46.117(b)(1); 21 CFR 5 0.27(B)(1)); or,

(2) A short form written consent stating that the elements of informed consent required as described above (conforming to 45 CFR 46.116; 21 CFR 50.25) have been presented orally to the subject or the subject's legally authorized representative (45 CFR 46.117(b)(2); 21 CFR 50.27(b)(2)).

When this method is used, there shall be a ***witness to the oral presentation***.

Also, the IRB shall approve a ***written summary*** of what is to be said to the subject or the representative.

Only the short form itself is to be signed by the subject or the representative.

The witness shall sign both the short form and a copy of the summary.

The person obtaining consent shall sign a copy of the summary.

A copy of the short form and a copy of the summary shall be given to the subject or the subject's representative.

The following is an example of a short form written consent. This sample was derived from current federal regulations as well as from information contained in a similar form provided by a subscription service from Management Concepts, Inc., Clinical Research Federal Rules & Regulations Manual, Vol. 1, Chapter 3 – Informed Consent Rules, page 3-31 (2002).

Consent to Participate in Research
Oral Presentation Short Form Consent

Title of Study:
Principal Investigator:
Sponsor/Institution:

You are invited to take part in a research study. Before you agree, we must tell you about the following:

1. The reason we are doing the research.
2. What we will do, and what your role will be, and how long you might be in the study; and, if you will be paid for your time and inconvenience.
3. If any part of the research is experimental (trying out a new idea).
4. Any risks or discomforts to you that we think might happen. We may also point out there may be risks we cannot predict at this time.
5. Any benefits you might get for taking part.
6. If there are ways that might help you other than to be in this research.
7. How we will keep information about you confidential.
8. If there is any available help to you in case you are injured by the research and if you will be responsible to pay for that help.
9. Reasons that we may have to ask you to drop out of the research.
10. If there might be costs you will have to pay to participate.
11. What happens if you decide you want to stop participating.
12. When we will tell you about new information that might affect your willingness to continue to take part.
13. How many people might be in the study.

Please ask questions at any time during our conversation.

If you agree to take part in this research, you will be given a copy of this form and a copy of a short summary of the research.

You may contact _____ at tel. _____ anytime you have further questions about this research.

You may contact _____ at tel. _____ if you have any questions about your rights as a research volunteer or what to do if you are injured.

Taking part in this research is voluntary and you are free not to take part or decide to drop out without any penalties or loss of benefits to you. Signing this form means that the research study has been explained orally to you and that you have voluntarily decided to participate.

_____ _____
Signature of Participant Date

_____ _____
Signature of Investigator or Authorized Personnel Date

_____ _____
Signature of Witness Date

My signature as witness certifies that the research study has been explained to the research volunteer in my presence, that he/she appears to understand the information, and that he/she signed this form by his/her own free will.

The following form is suggested as a written summary form to be approved by the IRB:

Short Form Consent Written Summary

Title of Study:

Principal Investigator:

Sponsor/Institution:

We have discussed this research project with you. We have gone over the details described in the consent form.

This research is about [***fill in a summary statement***]

Your role in the research will be [**describe briefly**]

Summarize the following:
We discussed some risks, benefits, how long you'll be in the study, costs and payments, any alternatives to being in the study that might be of benefit to you, and what might happen if you stop being in the study. Please ask any questions you may have at any time by calling the telephone numbers in the consent form. You will receive a copy of this written summary.

_____ _____
Signature of Investigator or Authorized Personnel — Date

_____ _____
Signature of Witness — Date

My signature as witness certifies that the research study has been explained to the research volunteer in my presence, that he/she appears to understand the information, and that this summary accurately reflects the discussion in the informed consent process.

c. Witness Requirements/Guidance

Other than the federal regulatory requirements as cited above, the IRB may recommend a witness to the informed consent process where the IRB finds either in full-board or expedited review that a witness to the informed consent process would be in the best interest of the research subjects. In reaching this recommendation, the IRB would take into consideration the categories of potentially vulnerable persons listed in I.G.4 of these guidelines and policies. Notwithstanding the federal

regulatory requirements, the IRB's recommendation of witness to the consent process may apply whether or not the informed consent process involves a comprehensive written document or is presented orally to the subject as described above.

The witness must directly observe the consent process and not merely be present during the signing of the document. The witness should be an impartial adult who has no interest in the research project and who cannot be unfairly influenced by the investigator or members of the research team. Ideally, the witness would be a person unaffiliated with the project or the investigator's academic department or research unit of the institution. However, a member of the research team who serves as a clinical monitor or is otherwise a research subject advocate may act as a witness to the informed consent process.

In no event may the investigator or other person authorized to conduct the informed consent process serve as the witness to the informed consent process.

The investigator may petition the IRB, with appropriate justification, that this requirement unfairly burdens the conduct of the research and that a member of the research team should be allowed to act as a witness to the consent process. Justification for this allowance should explain how the research team member's interest or involvement in the research would not bias his/her role as witness to the consent process.

d. Signed Consent Form Waiver

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all of the subjects, if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from 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*** (45 CFR 46.117(c)(1))***; or,***

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46.117(c)(2); 21 CFR 56.109((c)(1)).

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research (45 CFR 46.117(c)(1) & (2); 21 CFR; 21 CFR 56.109(b)).

The IRB will carefully examine requests for signed consent form waivers and may advise investigators to seek certificates of confidentiality where appropriate to protect subjects from disclosure of potentially harmful

information. The IRB will consider the nature of the information, protective measures taken to protect confidentiality as well as the degree of harm that may result from breach of confidentiality.

C. THE PROCESS AND DOCUMENTATION OF ASSENT OF MINORS AND PERMISSION OF PARENT(S) OR GUARDIAN(S)

1. Assent Process

Legally, children cannot give consent on their own behalf. In the context of research, the terms children and minors are used interchangeably. The permission of their parent(s) or a legal guardian is, therefore, required before children can participate in any non-exempt (and some exempt) research projects. In the State of Georgia, a minor attains majority at age 18 or upon marriage. Pregnancy does not confer majority status. A minor may, however, with IRB approval, legally consent on his/her own behalf (as a mature minor) if the research involves a treatment for which a minor's consent is permissible under applicable law (e.g., use of contraceptives, treatment for venereal disease or drug abuse).

If a subject under the age of 18 is legally declared to be emancipated he/she may consent to participate in research. **NOTE: The State of Georgia <u>does not</u> have an emancipated minor's act. Other than a court order, only marriage appears to act as an emancipating condition for any person under the age of 18 years. Becoming pregnant or becoming a parent does not confer emancipation in Georgia except for very limited conditions involving medical care (not research) and other essential contractual transactions.**

The IRB considers assent to involve a minor's affirmative agreement, either orally or in writing, to be a subject in research, after the research has been explained in a manner understandable to the minor considering the minor's age, educational level, maturity, medical and physical condition as well as psychological state. Failure to object to participate in research cannot be construed as assent (45 CFR 46.402(b); 21 CFR 50.3(n)). In most circumstances a minor's deliberate objection should be regarded as a veto to their involvement in the research. However, parents or guardians may, with IRB and investigator approval, override a minor's objections to interventions that hold the prospect of direct benefit to the minor.

Parental or legally authorized representative permission (e.g., "guardian") is considered to involve the elements of informed consent as required and described above. The IRB provides a template of such a permission form to be used in research involving minors as well as a suggested assent format. In any event, neither assent nor parental/legally authorized representative permission should be in any way coerced. The IRB will determine and advise investigators as to the process by which assent should be obtained and how assent should be documented (45 CFR 46.408(e); 21 CFR 50.55(g)).

The assent process should be approached as meaningfully as the consent process described above. Unless circumstances determine otherwise, assent should be obtained in the presence of and in discussion with the minor's parent(s) or legally authorized representative. The person obtaining assent should minimize any attitude or appearance conveying position of authority where otherwise the minor

may interpret the process as his/her having little meaningful choice as to participation.

In cases where the IRB determines that minors' assent should be sought and documented, it shall advise as to form and process. In making this determination the IRB will consider the duration of time minors are expected to participate, factors that may impact upon minors' capacity to assent, and factors relating to education, maturity, socioeconomic status, state of health, and risk/benefits of participation. Investigators are encouraged to provide the IRB with a plan for assent of minor subjects.

The following criteria are proposed as guidelines for seeking assent of minor subjects in research:

Age 6 years or younger: To the extent practicable, minors in this age range should be told about the research in terms understandable to them. They should be given an opportunity to ask questions and where practicable to view the research site, materials and procedures. The IRB will approve a script to be used to describe the research to minors in this age range. Parental or guardian permission must be obtained as explained below. The decision to participate would rest mainly with the parent/guardian.

Ages 7 to 13: For this age range the IRB recommends a written assent form at a reading level appropriate to the child's age. The assent form should provide an outline of what the subject will be asked to do and should emphasize the voluntariness of being a research subject. Each minor subject should read the assent form out-loud and explain to the investigator his or her understanding of what he or she read. The minor subject must be given an opportunity to ask questions and a reasonable opportunity to decide whether or not to participate in the research. Except as may be provided in regulatory requirements explained below, expressions of doubt or declinations expressed otherwise by the minor must be interpreted as refusal to participate and shall prevail even over the parents' or guardians' wishes to the contrary. This recommendation applies as well in cases where a child may enter a study at an age where assent is not required but attains age 7 while continuing to participate in the research.

Ages 14 to 17: For this age range the IRB recommends a written assent form with sophistication appropriate for high school students. The information contained in this assent process may resemble that contained in parent/guardian permission forms. Investigators may consider having minors in this age range sign the assent to impart a dimension of solemnity although this would have no legal bearing. The minors in this age range should be asked to explain their understanding of the research and be given ample opportunity to ask questions. Once again, except as may be provided in regulatory requirements explained below, expressions of doubt or declinations expressed otherwise by the minor must be interpreted as refusal to participate and shall prevail even over the parents' or guardians' wishes to the contrary.

Verbal assent may be appropriate in some circumstances. Investigators must clearly describe in IRB applications for review why a verbal assent process is appropriate and how it will be documented. In cases where verbal assent is approved by the IRB, the IRB will require the investigator to prepare a script to be read to the minor subjects. The parent(s)/guardian(s) shall receive a copy of the script with a written acknowledgement from the investigator as to the investigator's formed belief and judgment that the minor understands the nature of the research.

In cases where the IRB finds and documents that a waiver of assent is appropriate, the IRB will require the investigator to prepare a description of the research, written at the appropriate reading level of minor subjects, to be given to the subjects as well as a copy to be given to the parent(s)/guardian(s) as part of their permission process.

Any assent process approved by the IRB expires as indicated on notice of approval documentation or upon any minor subject attaining the age of majority while participating in research. Any minor attaining the age of majority (18 years old) while participating in research must consent to continue as an adult.

2. Regulatory Requirements - the DHHS

a. Research not involving greater than minimal risk.

"Risks" in this category of subjects is interpreted as those risks normally encountered during the daily life of average, healthy children living in safe environments or equivalent to the risks associated with the performance of routine physical or psychological examinations or tests (OHRP Secretary's Advisory Committee on Human Research Protections (SACHRP), Appendix B, 11/25/05). This standard is applicable as well to international studies. The minimal risk standard should be assessed and indexed according to the age(s) of the children.

SACHRP advises that research procedures involving children should be approved as "minimal risk" only if the probability and magnitude of harm are equivalent to or less than the risks of daily life or routine examinations with respect to duration of involvement, cumulative characteristics of risk factors, and reversibility of harm.

In this case, assent of the child and the permission of one parent or the child's legally authorized representative shall be considered sufficient (45 CFR 46.404; 408(b)). The SACHRP document provides examples of procedures considered as standards that meet the definition of minimal risks.

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

The IRB must find:

(1) The risk is justified by the anticipated benefit to the subjects (45 CFR 46.405(a)).

In reference to the SACHRP document cited above, the IRB considers the likelihood that the benefit will actually materialize, the anticipated magnitude of the benefit, and the degree to which anticipated benefits are at least as or superior to available alternative approaches, if any exist. The IRB shall base its assessment on sound scientific evidence provided by the investigator in the research protocol. Any procedures, tests or methods to be employed relative to anticipated benefit must be justified as an integral part of the research design and cannot be performed on speculation or the potential for a serendipitous beneficial outcome.

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by alternative approaches (45 CFR 46.405(b)).

The IRB shall carefully examine research procedures to determine whether the investigator has justified non-beneficial procedures as vital to the conduct of the research and that the parental permission document clearly explains the nature and rationale for such procedures. In cases where multiple procedures are proposed, the IRB shall assess each procedure individually as well as collectively to determine a reasonable relationship vital to the success of the research proposed.

In this case, assent of the child and the permission of one parent or legally authorized representative shall be sufficient, unless the IRB finds and documents that, in the best interest of the child, the permission of both parents, if reasonably feasible, should be obtained (45 CFR 46.405(c); 408(b)).

c. <u>Research involving greater than minimal risk and no prospect of *direct* benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.</u>

The IRB must find three conditions described below plus adequate provisions for soliciting assent of children and permission of their parents or guardians (45 CFR 46.406(d), as set forth in 45 CFR 46.408):

(1) The risk represents a minor increase over minimal risk (45 CFR 46.406(a).

Based upon sufficient evidence before it, the IRB must make a judgment as to the probability and magnitude of harm giving rise to a slight increase over minimal risk. Included in this judgment will be an analysis as to the nature and duration of potential harm as well as the probability of escalation of harm to greater than a minor increase over minimal risk. The IRB shall consider any

factors identified as minimizing risks. The term "condition" is interpreted by the SACHRP guidance described above to refer to specific physical, psychological, neurodevelopmental, or social characteristics known to negatively affect children's health or well-being or to increase their risk of developing a health problem in the future.

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social , or educational situations (45 CFR 46.406(b)).

In this context, "commensurate" means *similar* to those interventions or procedures that children with the condition or disorder, as a class, have or are expected to experience. However, "commensurate" does not justify any level of risk beyond a minor increase over minimal risk. For example, a procedure or intervention that would present an unfair burden to the subject would be considered one that elevates the risk level above what is permissible in this code section. Commensurability is to be judged by what the parent/child believes is commensurate in the child's particular circumstance. The risk assessment criteria remain as described under II.C.2.a. & b. above and must be justified in the protocol as being met and applicable for the study under review. The investigator must convincingly propose the interventions or procedures to be used in the study are similar to those that children with the condition or disorder, as a class, have or are expected to experience (SACHRP guidance, cited above).

(3) The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition (45 CFR 46.406(c)).

"Vital importance" is interpreted to mean clear and significant scientific evidence that procedures or interventions intended in the research are likely to yield generalizable knowledge that would contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration or treatment of a condition or disorder (SACHRP guidance cited above).

Clear and significant evidence, although subjective, must be deliberated by the IRB in order to reach a valid conclusion as to whether this criterion has been met. The IRB shall consider whether the scientific evidence demonstrates a substantially more likely than not probability that the research would result in generalizable knowledge to meet the standard of this code section.

Under this risk category, assent of the child and permission of ***both*** parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent

has legal responsibility for the care and custody of the child (45 CFR 46.408(b)).

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

This category of research is referred to as a "407 review" in reference to codification at 45 CFR 46.407. This is a special categorization of research involving action to be taken by the Secretary of DHHS (45 CFR 46.407(b)). The IRB is required to make specific findings before submitting a protocol to HHS for consideration of a 407 review. The process for such a review involves the following steps:

(1) The IRB must determine that the protocol does not meet the conditions for approval of research under 45 CFR 46.404, 405 or 406 as described above.

(2) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children (45 CFR 46.407(a)).

(3) The IRB determines that the proposed research and the parental permission and assent process, forms and documentation meet regulatory requirements and are otherwise approvable under 45 CFR 46.408.

(4) The IRB or the institution may request that OHRP, on behalf of the Secretary of DHHS, conduct a section 46.407 review. In such a case, the IRB shall follow recommendations and requirements as described in OHRP guidance: "Special Protections for Children as Research Subjects – Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process" dated May 26, 2005 or as may be subsequently amended.

e. Waiver of parental permission requirements.

The IRB may determine that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children). In such case, the IRB may waive parental permission/consent requirements described above, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status and condition (45 CFR 46.408(c)).

The IRB may suggest consultation with a suitable individual knowledgeable about the research context and the rights and welfare of children.

f. Documentation of parental permission.

Permission by parents or guardians shall be documented in accordance with and to the extent required for informed consent (45 CFR 46.117) as described in these guidelines under II.B.2. (45 CFR 46.408(d)).

g. Documentation of assent.

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented (45 CFR 46.408(e)).
A person who commences in research under the legal status of being a minor must provide consent to continue as a subject in research upon becoming an adult (generally, on their 18th birthday).

h. Waiver of assent.

The IRB may determine that assent may be waived under circumstances in which consent may be waived in accord with 45 CFR 46.116 (45 CFR 46.408(a)). In such cases as it determines a waiver of assent is appropriate, the IRB will document its findings and justification.

i. Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 46.407 only if such research is:

(1) Related to their status as wards (45 CFR 46.409(a)(1)); or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards (45 CFR 46.409(a)(2)).

If the research is approved under 45 CFR 46.409(a), the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in *loco parentis*. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in , and agrees to act in, the best interest of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role of advocate or member of the IRB) with the research, the investigator(s), or the guardian organization (45 CFR 46.409(b)).

3. Regulatory Requirements – the FDA

a. Clinical investigations not involving greater than minimal risk.

For purposes of reviewing and approving research involving clinical investigations this category, the IRB will find and document adequate provisions for solicitation of assent of the children and permission of their parents or guardians (21 CFR 50.51). The determination and description of risk involved in this category of research is the same as described under II.C.2.a. in these IRB guidelines and policies.

In this case, assent of the child and the permission of one parent or the child's legally authorized representative shall be considered sufficient (21 CFR 50.55(e)(1)). The SACHRP document referenced above provides examples of procedures considered as standards that meet the definition of minimal risks. The FDA regulations define minimal risk as : …the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (21 CFR 50.3(k)). Documentation of parental/guardian permission shall conform to the requirement set forth under 21 CFR 50 Subpart B.

b. Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

For purposes of reviewing and approving research involving clinical investigations in this category in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, the IRB will find and document:

(1) The risk is justified by the anticipated benefit to the subjects (21 CFR 50.52(a)).

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches (21 CFR 50.52(b)).

In this case, assent of the child and the permission of one parent or legally authorized representative shall be sufficient (21 CFR 50.55(e)(1)), unless the IRB finds and documents that, in the best interest of the child, the permission of both parents, if reasonably feasible, should be obtained.

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

For purposes of reviewing and approving research involving clinical investigations in this category in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, the IRB will find and document:

(1) The risk represents a minor increase over minimal risk (21 CFR 50.53(a)).

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations (21 CFR 50.53(b)).

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding of amelioration of the subjects' disorder or condition (21 CFR 50.53(c)).

(4) Adequate provisions are made for soliciting the assent of the children an permission of their parents or guardians (21 CFR 50.53(d)).

Under this risk category, assent of the child and permission of *both* parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (21 CFR 50.55(e)(2)).

d. Clinical investigations not otherwise approvable that present an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children.

This category of research (21 CFR 50.54) is similar to that referred to as a "407 review" in section C.2.d. above. This is a special categorization of research involving action to be taken by the Commissioner of the FDA following an opportunity for public review and comment (21 CFR 50.54(b)). The IRB is required to make specific findings before submitting a protocol to the FDA for consideration of a section 50.54 review. The process for such a review involves the following steps:

(1) The IRB does not believe that the clinical investigation falls within the scope described in 21 CFR 50.1 and 21 CFR 56.101 and involving children as subjects does not meet the requirements or 21 CFR 50.51, 50.52, or 50.53 as described above (21 CFR 50.54).

(2) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious

problem affecting the health or welfare of children (21 CFR 50.54(a)).

(3) The Commissioner of the FDA makes regulatory determinations as required by 21 CFR 50.54 (b)(1),(2).

e. Parental permission and assent requirements.

The IRB must determine that the permission of each child's parents or guardian is granted (21 CFR 50.55(e)) as described above in these guidelines in reference to specific research risk categories.

The IRB must determine that adequate provisions are made for the soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent (21 CFR 50.55(a). In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate (21 CFR 50.55(b)). The IRB shall consider other factors including but not limited to education level, reading ability, and general state of health in deciding the appropriate form and format for seeking assent of children.

f. Documentation of parental permission.

Permission by parents or guardians shall be documented in accordance with and to the extent required for informed consent (21 CFR 50.20; 50.25) as described in these guidelines under II.B.2.

g. Documentation of assent.

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented (21 CFR 50.55(g)).

h. Exceptions and waiver of assent.

The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted (21 CFR 50.55(c)(1); or,

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation (21 CFR 50.55(c)(2).

(3) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(a) The clinical investigation involves no more than minimal risk to the subjects (21 CFR 50.55(d)(1));

(b) The waiver will not adversely affect the rights and welfare of the subjects (21 CFR 50.55(d)(2));

(c) The clinical investigation could not be practicably carried out without the waiver (21 CFR 50.55(d)(3)); and,

(d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation (21 CFR 50.55(d)(4)).

i. Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 21 CFR 50.53 or 50.54 only if such clinical investigations are:

(1) Related to their status as wards (21 CFR 50.56(a)(1)); or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards (21 CFR 50.56(a)(2)).

If the research is approved under 21 CFR 50.56(a), the IRB must require appointment of an advocate for each child who is a ward (21 CFR 50.56(b). The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in *loco parentis* (21 CFR 50.56(b)(1)). One individual may serve as advocate for more than one child (21 CFR 50.56(b)(2)). The advocate must be an individual who has the background and experience to act in , and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation (21 CFR 50.56(b)(3)) The advocate must not be associated in any way (except in the role of advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization (21 CFR 50.56(b)(4)).

D. ADDITIONAL PROTECTIONS FOR OTHER CLASSES OF RESEARCH SUBJECTS CONSIDERED TO BE POTENTIALLY VULNERABLE

As expressed in these guidelines and policies under I.G., the IRB considers the following categories of persons and factors in determining whether additional protections may be required.

- Employees
- Students at any level of education
- Economic status
- Education level in general

- Physical or medical disability/compromise
    - Mental capacity/compromise:
        Cognitive impairment/mental disease
        Influence of medication
    - Sensory impairment/sight/hearing
- Relationship between investigator and subject
- Cultural/ethnic origin and customs
- Social stigmatization
- Colloquial issues

The IRB will advise investigators as to measures it considers necessary to afford additional protections (45 CFR 46.109(b); 45 CFR 46.111(a)(6),(7); (b); 21 CFR 56.109(b); CFR 21.56.111(a)(6),(7); (b)). Such measures may include specific advice as to additional consent requirements, e.g., larger print for the visually impaired, compensation for participation likely to be viewed as coercive for economically disadvantaged persons, and whether data gathering includes information of sufficient sensitivity as to warrant obtaining a certificate of confidentiality, if available from the sponsor.

More specifically, the IRB requires the following additional protections for the following categories of human subjects:

1. Students at Morehouse School of Medicine (MSM)

For research intending to recruit Morehouse School of Medicine students as subjects, the IRB will consult with the dean for student affairs. The dean for student affairs will advise the IRB as to the suitability of the research, suggest modification to the research plan, or other suggestions as may be appropriate prior to IRB review and action on the research.

a. <u>Recruitment</u>

(1) For research involving MSM students as a body or class conducted by MSM personnel, potential student subjects should be approached as a body, e.g., class, assembly, etc., or through general announcements. Recruitment of students should be monitored by a third party not associated with the research. Third party personnel from either the office of student affairs or the department of medical education would be considered appropriate monitors.

(2) For research involving MSM students as a class or body conducted by personnel not associated with MSM, the office of student affairs will make appropriate arrangements for recruiting student involvement.

(3) For research involving MSM students as individuals, e.g., enrollment in a clinical trial, potential student subjects should be recruited through general announcements not directed at students in particular.

b. Consent Process

(1) For research involving MSM students as a body or class, the consent process should be conducted by individuals other than the investigator or a member of the research team where the project involves students who are in classes conducted by the investigator. The IRB may find an exception to this recommendation where the research involves the investigator's teaching methods and the curriculum is structured so as to make student participation required to conduct the research.

(2) For research involving MSM students as individuals and where the investigator is not the student's teacher or mentor, consent to participate in research should be conducted by the investigator or appropriately appointed member of the research team.

(3) For research involving MSM students as individuals and where the investigator is the student's teacher or mentor, consent to participate in research should be conducted by a person other than the investigator and monitored by a research subject advocate.

c. Nature of Research

(1) Unless research involving MSM students pertains to instruction or curriculum in which students must participate as required for course credit, research should not be conducted during any time assigned for classes, except as may be determined appropriate by the dean of academic affairs.

(2) In situations where the research offers extra credit to student participants, there must also be a reasonable alternative to gain extra credit for those students who decline to participate. The alternative effort afforded to students must equitably compare in terms of time, effort and reward.

(3) In cases where the research provides the student an opportunity to participate, the student must be informed that participation is voluntary, that there will be no penalty or unfavorable treatment should the student decide not to participate and that the student is free to withdraw participation without penalty at any time during participation. In cases where students decide to withdraw following agreement to participate, the students must be afforded an alternative to earn the extra credit as explained in c.(2) above.

(4) Reward of extra credit must be reasonably related to the time and effort required in the research or the alternative(s) to participate and must not be over-reaching such as to be considered coercive.

(5) Students may participate in research that may be considered to be greater than minimal risk, e.g., surveys or questionnaires designed to record information of a personally sensitive nature only where

the IRB, in consultation with the dean of academic affairs, determines that safeguards in the protocol sufficiently protect students' privacy by maintaining adequate security of confidential information.

(6) In cases where research involves students' academic records, the IRB will consider such research only after the dean of academic affairs, in consultation with the registrar, determines that such research is designed appropriately and in accord with current controlling federal and state laws and regulations governing the use of information recorded in official academic records.

(7) MSM students are free to participate in research endeavors designed to recruit a general population of subjects as would be any adult among the general population. The IRB will consider the nature of the research and investigative personnel in relationship to the students' academic environment.

2. Students at Other Institutions

Research intending to recruit students at any school location requires the approval of a signatory official of the school. If the school has an IRB, the IRB of the school must approve the research or the school must defer responsibility of IRB oversight to Morehouse School of Medicine.

In any school system or school location involving minors, the IRB, where it deems appropriate, will request the opportunity for parents to review all research materials to which their children would be exposed. The role of the school and its personnel will be carefully examined to determine that there will be no undue influence in recruitment of students or consequences adverse to their interests should they decide not to participate.

In reviewing research in this category, the IRB will consider appropriate steps as described above in II.D.1.

3. Employees

Employees of the institution may participate as subjects in research conducted at or by the institution. In reviewing research in this category, the IRB will carefully consider the relationship between the employee and the investigator/research team. The IRB will determine that such relationships do not impart coercion to participate or otherwise impact negatively on any employee deciding not to participate.

Employees should be recruited through general announcements and not approached individually as a matter of convenience. Employees are not to be offered incentives relating to their job performance or any factors impacting on potential advancement in their employment.

4. Adult Persons with Compromised Decision-making Capacity

The ethical principal of respect for persons demands that individuals be given an opportunity to consent, or assent, to the greatest extent possible considering their ability to do so. In considering consent in persons deemed to be cognitively impaired, the IRB adopts recommendations made by the Alzheimer's Association as expressed in "Research Consent for Cognitively Impaired Adults: Recommendations for institutional review boards and investigators," Alzheimer's Disease and Associated Disorders, Vol. 18 No. 3, July – September 2004: 171-175. Research in this category of persons need not only involve the study of conditions resulting in cognitive impairment but may involve research unrelated to compromised decision-making capacity for which a cognitively impaired subject may otherwise qualify as a participant.

The terms decision-making capacity, mental competency, and compromised capacity defy precise definition. For guidance, the IRB looks to learned sources and current law. In the State of Georgia, "…. 'inability of any adult to consent for himself' shall mean a determination in the medical record by a licensed physician after the physician has personally examined the adult that the adult 'lacks sufficient understanding or capacity to make significant responsible decisions' regarding his medical treatment or the ability to communicate by any means such decisions" (OCGA 31-9-2(c)). Although not specifically addressing research contexts, this description relates to a person's ability to understand information sufficiently to make responsible decisions; or, even in cases where the person may understand, is nonetheless incapable of communicating what is understood.

In a legal context, capacity refers to the ability to understand, appreciate and form a rational intention with respect to some act. Capacity may also refer to a codified legal standard such as a person must be 18 years or older to be considered to as an adult. Incompetence means failing a legal test of capacity as applied to specific situations. Capacity is generally destroyed by conditions, e.g., insanity, intoxication, trauma, etc. that alter one's ability to perform a particular legally recognized act. In brief, legal competency refers to a person's capacity to engage in an act at the time of evaluation.

In the research context, capacity would refer to the person's ability to understand their role in the research design and to express that understanding through competent decision-making and expressing their choice. When cognitive impairment interferes with capacity, the law looks to legally-authorized representatives (LAR) to assist in decision-making. Although the Georgia Medical Consent Law (OCGA 31-9-1) does not specifically mention "research," the IRB regards this law as sufficiently broad to include research. The text of the current law regarding authorization and empowerment to consent is reproduced here:

31-9-2

(a) In addition to such other persons as may be authorized and empowered, any one of the following persons is authorized and empowered to consent, either orally or otherwise, to any surgical or medical treatment or procedures not prohibited by law which may be suggested, recommended, prescribed, or directed by a duly licensed physician:

(1) Any adult, for himself, whether by living will or otherwise;

(1.1) Any person authorized to give such consent for the adult under a health care agency complying with Chapter 36 of Title 31, the 'Durable Power of Attorney for Health Care Act';

(2) In the absence or unavailability of a living spouse, any parent, whether an adult or a minor, for his minor child;

(3) Any married person, whether an adult or a minor, for himself and for his spouse;

(4) Any person temporarily standing in loco parentis, whether formally serving or not, for the minor under his care; and any guardian, for his ward;

(5) Any female, regardless of age or marital status, for herself when given in connection with pregnancy, or the prevention thereof, or childbirth;

(6) Upon the inability of any adult to consent for himself and in the absence of any person to consent under paragraphs (2) through (5) of this subsection, the following persons in the following order of priority:

(A) Any adult child for his parents;

(B) Any parent for his adult child;

(C) Any adult for his brother or sister; or

(D) Any grandparent for his grandchild.

(b) Any person authorized and empowered to consent under subsection (a) of this Code section shall, after being informed of the provisions of this Code section, act in good faith to consent to surgical or medical treatment or procedures which the patient would have wanted had the patient understood the circumstances under which such treatment or procedures are provided.

(c) For purposes of this Code section, 'inability of any adult to consent for himself' shall mean a determination in the medical record by a licensed physician after the physician has personally examined the adult that the adult 'lacks sufficient understanding or capacity to make significant responsible decisions' regarding his medical treatment or the ability to communicate by any means such decisions.

The IRB recognizes that most potential research subjects considered to be partially or totally cognitively impaired will unlikely have legally valid health care advanced directives. In cases where such directives are available, it is highly unlikely they would include permission for the LAR to enroll the person in research. The IRB also recognizes that the care of cognitively impaired persons may be relegated to persons who are competent but who are not LAR and may not be under the direct supervision of LAR.

Considering the Alzheimer's Association's recommendations for institutional review boards and investigators, the IRB provides the following directives:

a. Description /Nature of Research and Capacity Assessment

The investigator will describe in the application for IRB review the following:

(1) The rationale for the inclusion of cognitively impaired research subjects, including why it may be in the best interest of the subjects to participate.

(2) The process through which subjects' cognitive capacity is assessed and documented.

(3) A risk/benefit analysis of the proposed research.

(4) A description of the process for allowing potential subjects to provide affirmative acknowledgement to participate and how the investigator may determine when the subject declines participation regardless of the LAR's point of view.

b. Description of LAR

The investigator will provide the following information in the application for IRB review:

(1) The relationship of the LAR to the subject that will be considered appropriate to allow proxy consent in the context of the research.

(2) The role of designated caregivers in cases where the LAR is not the subject's caregiver.

(3) The process for assessing the LAR's basis of knowledge of the potential subject with regard to values, wishes and beliefs held or expressed by the subject during a time when the subject possessed competent autonomy.

c. Capacity Impairment in the Course of Research

The investigator will provide in the IRB application for review a plan for reassessing cognitive capacity where subjects may be susceptible to loss of full capacity following autonomous consent to participate. In cases where there is a reasonable probability that subjects are likely to experience a significant change in cognitive function, subjects should be given the opportunity to appoint a LAR prior to enrollment in research.

d. Regaining Capacity During the Course of Research

Subjects who were enrolled in research through a proxy consent process must be presented with an autonomous informed consent process for

continuation in the study in cases where the subject regains capacity at any time during the research.

e. The IRB Review Process

In its review and evaluation for approval of research involving cognitively impaired adult subjects, the IRB shall adopt the categories and stipulations for approval of research described under II.C.2 & 3., above as applicable to this category of research subjects. In the case of research in cognitively impaired adults, the designated LAR substitutes for "parent(s)" or "guardians" as described in the context of research involving children.

E. HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 – "HIPAA"

Under the HIPAA privacy regulations, 45 CFR 164.508(b)(3)(i), the Morehouse School of Medicine IRB does not require HIPAA authorizations for use or disclosure of protected health information to be combined with other regulatory requirements regarding informed consent to participate in research. It is the policy of the IRB to request investigators to use stand-alone HIPAA authorizations permitting the use and disclosure of individually identifiable health information. The IRB need not approve stand-alone HIPAA authorizations.

The IRB defers to the responsibility of each covered entity under 45 CFR 160 and 164 to comply with use and disclosure requirements, including waivers and uses and disclosures for which authorization is not required as permitted under 45 CFR 164.512(i)(1)(i). A covered entity is basically the organization, unit or individual having custodianship of individually identifiable protected health information. (Reference: Guidance for Industry, IRB Review of Stand-Alone HIPAA Authorizations under FDA Regulations, October 21, 2003). For more information concerning institutional requirements of the HIPAA, investigators are referred to the institutional Compliance Office of Clinical Affairs.

The IRB shall consider review and approval of requests for HIPAA consent waivers as follows:

Authority: 45 CFR 164 - - Security and Privacy – Subpart E – Privacy of Individually Identifiable Health Information – Section 164.512 – Uses and disclosures for which an authorization or opportunity to agree or object is not required.

45 CFR 164.512(i)(2)(i) – The information contained in item (ii) below shall be reviewed by the Morehouse School of Medicine IRB to determine, by either full-board or expedited review, the suitability of alteration or waiver of authorization.

45 CFR 164.512(i)(2)(ii) - The Morehouse School of Medicine IRB shall consider approval of the alteration or waiver, in whole or in part, upon satisfaction of the following criteria described in the investigator's application for review:

1. The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based upon, at least, the presence of the following elements;

   a. An adequate plan to protect the identifiers from improper use and disclosure;

   b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and,

   c. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

2. The research could not practicably be conducted without the waiver or alteration; and,

3. The research could not practically be conducted without access to and use of the protected health information.

4. A description of the protected health information required for the conduct of the research.

SECTION III
IRB ADMINISTRATION
IRB OFFICE, COMMITTEE, ADMINISTRATIVE FUNCTIONS
AND
EDUCATION

A. ORGANIZATION

The IRB is administratively positioned in the Office of Research Development under the Office of the Dean & Senior Vice president for Academic Affairs. The institutional signatory official for the IRB is the Vice President & Associate Dean for Sponsored Research Administration. The IRB is a standing committee of the Academic Policy Council (Bylaws of the Faculty, October 30, 1998, Article V, Section 4, K.). Policies and procedures relating to IRB functions reflect requirements of current federal regulations (45 CFR 46, 21 CFR 50, 21 CFR 56, 45 CFR 164), advisory memoranda of federal agencies, laws of the State of Georgia, and Morehouse School of Medicine institutional policies.

B. COMMITTEE MEMBERSHIP, ADMINISTRATION AND FUNCTION

Institutional IRB members are appointed to serve on the IRB through the Office of the Dean & Senior Vice President for Academic Affairs upon recommendation made by the IRB chair, members currently serving on the IRB and as may be recommended through the Academic Policy Council. IRB membership conforms to current federal regulations and federal agency requirements governing the conduct of research on human subjects (45 CFR 46.107, 307; 21 CFR 56.107). Faculty and staff of Morehouse School of Medicine may request to serve on the IRB. Membership on the IRB is established to operate in an academic calendar year (July 1st through June 30th). Members are appointed for an initial 3 year term and may serve additional terms at their request. The chair of the IRB is appointed by the Dean and Senior Vice President for Academic Affairs upon recommendation from the Committee on Committees. The membership of the IRB includes a balance of physicians, other health care professionals and basic scientists representing broad professional expertise in research areas of interest to the institution as well as non-scientists having expertise in a variety of areas (e.g., administration, education, ethics, law, sociology, social work, theology). Persons not affiliated with the institution may be recommended for membership by the IRB chair or IRB members to the Dean and Senior Vice President for Academic Affairs. Unaffiliated members are reappointed on a yearly basis and serve as long as they wish. The deliberations and reviews conducted by the IRB membership are strengthened by representation of a diverse group of academic and community professionals and lay people who represent gender balance, an equitable representation of ethnic/racial composition, and a multidisciplinary perspective. By virtue of their attributes and training, the IRB membership enhances the level of cultural competency skills and sensitivity appropriate to the research subject community which it serves.

The IRB administrator may also serve as a voting member of the IRB and has signatory authority under the direction of the chair to sign office correspondence and letters of approval of research. The chair of the IRB may appoint a vice chair, may ask the membership for a volunteer for vice chair or may ask the members to elect a vice chair. The vice chair shall have IRB signatory authority. The IRB administrator or vice chair may act as chair to conduct meetings.

The IRB meets once a month at regularly scheduled dates and times. Meeting frequency may change depending upon institutional circumstances and requirements. Meeting dates and times are well publicized. The chair of the IRB, or in his/her absence the IRB administrator or vice chair, may convene called meetings as necessary to conduct urgent business. Matters of pecuniary interest are not considered reasons sufficient to convene called meetings. Investigators submitting protocols are not requested to attend meetings unless deemed essential to the deliberations. Investigators who may also be members of the IRB are excused from deliberations and the voting process of their protocols submitted for review.

At the commencement of each convened meeting, the IRB administrator, chair, vice chair or a member designated by the chair shall confirm the assembly of an appropriately configured quorum to conduct business. Minutes of meetings shall be recorded by the administrator, chair, vice chair or a member designated by the chair. Administrative office staff may assist in recording IRB minutes.

Protocols requiring full-board review are presented by the primary reviewer; and, when a secondary reviewer has been assigned, the secondary reviewer provides input as well. Upon conclusion of their presentation, the reviewers make a recommendation based upon their findings. Each member present is then allowed an opportunity to ask questions, raise issues, and make comments. The IRB chair will provide the committee with information from members who could not make the meeting but who submitted input to the IRB office. Following close of discussion, the person chairing the meeting asks the reviewer to make a motion. A motion may be made to approve, to table action pending further considerations, or to disapprove the research study. Upon a motion made and seconded, the chair calls for the question; provided there is no further discussion requested, votes are cast by a show of hands. Unless otherwise indicated by the IRB, approvals are issued for a period not to exceed one-year. On continuing review approvals, the inclusive dates of re-approval represent a continuum of time from the expiration date of the initial review approval but in no case will extend beyond one year from the expiration date of the initial approval period. Motions are carried or defeated by a majority vote of the quorum present. Abstentions do not count for or against a motion. In cases where abstentions exceed the number of votes required to carry or defeat a motion, the chair calls for a motion to table action pending further considerations.

IRB members receive a copy of the minutes along with the agenda for the next meeting as soon as practicable before the next scheduled meeting. Administrative matters and expedited reviews conducted between meeting dates are reported to members by way of entries on the meeting agenda or are announced as matters of other business during convened meetings. IRB members receive copies of applications for review as well as consent forms to be discussed at convened meetings two weeks or more prior to each meeting. There may be some exceptions where exigent circumstances, e.g., compliance issues, demand a shorter period of time.

Approval of minutes and action on protocols requiring review at convened meetings will be conducted in compliance with 45 CFR 46.108(b); 21 CFR 108(c), ensuring a majority

of IRB members are present, including at least one member whose primary concerns are in nonscientific areas, and assuring approval of research by a majority vote of those members present at the meeting. The IRB shall record the number of votes for a motion, votes opposed to a motion, and abstentions to a motion. Reasons for votes opposing a motion will be recorded in the minutes. No IRB member may participate in initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e); 21 CFR 56.107(e)). Being a member of a department, center or unit in which a protocol is under IRB review does not unto itself constitute a conflict of interest. Upon finding a member has a conflict of interest, including but not limited to personal, financial or professional reasons, or upon a member's acknowledgment of a conflict of interest, the member will be excused or will abstain from the voting process.

C. IRB OFFICE FUNCTIONS

1. Protocol Intake

Investigators may submit initial applications for IRB review at any time. Upon receipt of applications, the IRB administrator or office staff reviews the material for completeness. The IRB administrator assigns a protocol number and initiates an intake and tracking record. IRB records may be kept in computerized file systems in addition to physical document file systems. The IRB administrator (if also serving as a member of the committee), chair, or vice chair reviews the research file to determine whether the protocol may be reviewed by expedited process or requires review at a convened IRB meeting. Upon determining the file is complete and the appropriate level of review, the IRB office acknowledges receipt of the file and informs the investigator of an approximate schedule of review. The IRB administrator, chair or vice chair assigns the file to a primary IRB member reviewer with a suggested date of completion of feed-back to the IRB office. A secondary reviewer may also be assigned at the discretion of the IRB administrator, chair, or vice chair. At its discretion, the IRB may also invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may present findings at meetings but may not vote with the IRB (45 CFR 46.107(f); 21 CFR 56.107(f)).

To the greatest extent possible, the IRB offers investigators a preview of applications. The purpose of the preview is to assist in perfecting the application so as to facilitate a timely and less complicated review process. For protocols requiring full-board initial or continuing review, the IRB seeks applications 30 days in advance of published meeting dates. Although the 30 day advance period is not considered a deadline, it assures a greater opportunity to conclude approval at the earliest convened meeting.

2. Protocol Review Management

As detailed in I.B. and C. of these guidelines and policies, reviews are expected to be completed in a timely manner. In no case, however, will time constraints override the importance of careful and complete review processing. Timeliness of reviews depends upon completeness and clarity of material submitted for review as well as the complexity of the research under review. Primary and secondary reviewers fill out review checklists and documentation forms as well as forms requesting responses from investigators. Reviewers may direct their questions and comments to investigators with copies to the IRB office or the IRB office will direct reviewers' questions to investigators. Investigators are given a reasonable time to answer review queries. The IRB strives to complete reviews within 15 to 30 days following receipt of applications for review.

For applications requiring action at convened IRB meetings, following reviewer(s) satisfaction of answers to questions raised and comments addressed, the review application and preliminary findings are forwarded to IRB members for deliberation at the meeting. The IRB office attempts provide IRB members with applications for review, consent forms and reviewer input, when reasonably available, at least two weeks prior to scheduled meeting dates. In some cases, shorter periods of time prior to meetings may be unavoidable.

For applications determined suitable for expedited review, following reviewer(s) satisfaction of answers to questions raised and comments addressed, the reviewer(s) notify the IRB office that the review is complete and give(s) their recommendation for approval or that issues raised in the review process should be addressed by the convened IRB.

3. Post Review Activities

The IRB office notifies investigators of the outcome of convened meeting reviews within one week following the meeting. For studies that were tabled, the IRB office provides investigators with the deliberation outcome and input on issues raised by the committee for the investigator to consider resolving prior to the study being resubmitted for reconsideration.

Minutes are transcribed by the IRB administrator or office staff and presented to the chair for review and editing.

The IRB administrator records the study status on the intake and tracking record and places a copy of approval letters in a tickler file used to track continuing report due dates. A tickler information system may also be kept in an electronic database. The IRB administrator sends report(s) due notices to investigators, generally 45 - 30 days in advance of the expiration of project approval dates.

4. Protocol Modifications and Other Communications

Protocol amendments and other research-related communications are reviewed by the IRB administrator or chair and managed according to review guidelines described in appropriate sections of these guidelines and policies. Investigators are on notice not to commence research modifications without prior approval from the IRB unless justified for reasons necessary for the safety and welfare of research subjects.

5. Administrative Authority

The chair of the IRB may hold academic and other appointed titles as determined appropriate by the administration and function of the institution. The IRB chair has the administrative authority to carry out the following activities:

a. Construct and revise forms required in the process of IRB review.

b. Make changes to the IRB guidelines and policies as may be required by laws, regulations, agency directives, institutional policy or as otherwise appropriate to enhance its operation or obligation in the protection of human research subjects.

c. Directly communicate with legal counsel where required to resolve issues beyond the training, experience, education or knowledge from within its membership or within the institution. The IRB chair will notify the appropriate institutional authority of the need and intention to seek external legal counsel.

d. Maintain research file security and appropriate level of confidentiality of proprietary information by restricting access to file information except as required by laws, regulations or by its membership in the review process.

e. Conduct or direct appropriate individuals to conduct IRB file audits to ensure compliance with regulations and policies.

f. Directly communicate with federal and other agencies and bodies to seek advice in matters pertaining to IRB functions, institutional responsibilities and issues pertaining to protection of human research subjects.

6. Collegial Activities

The IRB administrator, chair, vice chair or members offer their colleagues personal assistance and advice in filling out applications for review, writing informed consent/assent documents, complying with regulations and guidelines, as well as the design and execution of research protocols required to address

human subjects research. Upon invitation, IRB representatives will participate in seminars, workshops and classroom discussions on matters pertinent to education on research involving human subjects.

7. Website Management

The IRB administrator and office staff maintain an institutional website devoted to the institution's human subjects protection program. Investigators and other interested parties may obtain information, forms, and access to pertinent human subjects research websites.

D. TRAINING & EDUCATION

IRB members and research personnel must pass select modules of the Collaborative IRB Training Initiative (CITI) Course in the Protection of Human Subjects hosted at the University of Miami. Both initial and continuing education modules are required as published from time-to-time by the IRB office.

The IRB office staff conducts new member training sessions. To the extent practicable, new members assigned to conduct reviews are paired with experienced members until they gain proficiency in the review process.

The IRB is available to participate in graduate education courses, seminars and workshops.

The IRB office maintains a current library of books and periodicals pertinent to the conduct of research involving human subjects.

The institution encourages IRB members and human subjects research personnel to attend local and national meetings of topical interest on human subjects research.

The institution encourages IRB members and human subjects research personnel to join professional organizations such as the Applied Research Ethics National Association (ARENA), Public Responsibility in Medicine and Research (PRIM&R), and the American Society of Law, Medicine and Ethics (ASMLE).