Table of Contents

MOLLOY UNIVERSITY IRB MANUAL

List of Appendices

Appendix A: Belmont Report

Appendix B: DHHS Regulations 45 CFR 46 (2018 Requirements)

Appendix C: FDA Regulations 21 CFR 50

Appendix D: FDA Regulations 21 CFR 56

Appendix E: Additional Info on FDA-Regulated Research

- **Investigational Products in Clinical Investigations (Clinical Trials)**
- **Expanded Access to Investigational New Drugs**
- **Open Label Protocol or Open Protocol IND**
- **Treatment IND**
- **Group C Treatment IND**
- **Parallel Track**
- **Emergency Use IND**
- **Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices**
- **Use of Investigational Products when a Subject Enters a Second Institution Personal**
- **Importation of Unapproved Products**
- **Food and Drug Administration (FDA) Classification of Drug Studies**
- **Exception from Informed Consent for Studies Conducted in Emergency Settings**

Appendix F: Guidelines for Preparing a Research Protocol

Appendix G: Certificates of Confidentiality

GENERAL INFORMATION

The policies and procedures outlined in this manual apply to:
1. All research conducted by or under the direction of a Molloy University (MC) employee, faculty member, or student whether the research is funded or non-funded, or any research conducted by, or
2. under the direction of a Molloy University employee or faculty member utilizing Molloy property, personnel, students or facilities, or
3. any research that utilizes the institution's emails or contact information from the Molloy University website or non-public information to identify or contact human research subjects or prospective subjects.
4. IN ADDITION TO THE IRB'S RESPONSIBILITIES FOR HUMAN SUBJECTS' (HS)RESEARCH PROTECTIONS, NON- HS INVESTIGATIVE ACTIVITIES NEED TO BE SUBMITTED (VIA IRBNET) TO THE IRB FOR DETERMINATION AND COMPLIANCE WITH MOLLOY IRB POLICIES PRIOR TO THE START OF THE ACTIVITY.

According to DHHS regulations (45 CFR)

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

The following activities are deemed not to be Research

1) Scholarly and journalistic activities (e.g. oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focuses directly on the specific individuals about whom the information is collected.
2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or manmade disasters)
3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4) Authorized operational activities in support of intelligence, homeland security, defense, or other national security missions.

Human Subject means a living individual about whom an investigator (whether professional or student) conducting research (i) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses,

studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Clinical Trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

According to FDA regulations (21 CFR)

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

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

These policies also apply to any outside individuals who engage in research with human subjects at the University or any of its facilities.

Introduction to the Institutional Review Board

The Institutional Review Board (IRB) is a committee comprised of Molloy faculty, administrators, scientists, non-scientists, and community members whose purpose is to ensure that the rights and welfare of human subjects are protected in all medical, behavioral and social sciences research. In accordance with federal and state regulations governing research, an IRB must review and approve research involving human subjects prior to its initiation. It is the responsibility of the IRB to determine whether proposed research exposes subjects to unreasonable or unnecessary risk, to review informed consent forms and process, and to monitor the progress of research. In its deliberations, the IRB will use the ethical principles as detailed in the Belmont Report (1979) to make its determination. A copy of the Belmont Report is provided in the appendix. The IRB is the primary designated IRB for the University, and its membership is in accordance with federal policy. Outside IRB review will be accepted when required for compliance with the single IRB mandate, or when MC IRB Chair approves the reliance on another IRB for a specific protocol.

MC IRB maintains a Federal Wide Assurance (FWA) and, prior to the implementation date of the 2018 requirements, “checked the box” to extend

the provisions of 45 CFR 46 to all research. Going forward the provision to allow an institution to check the box will no longer be available, but it is the intent of MC IRB to continue to maintain the same standard for all research as outlined in 45 CFR 46 (2018 requirements).

Members of the IRB and the Chair are appointed by the Vice President for Academic Affairs from the volunteers without a limit to term of appointment). There is no remuneration for individuals serving as IRB members. No IRB member participates in the review of any study on which s/he is an investigator or co-investigator or where a potential for conflict of interest exists.

All IRB members will be trained in human subject protections. Continuing education activities will keep members current on regulations and other issues related to their IRB duties.

The IRB may, at its discretion, invite individuals with competence in special areas (consultants) to assist in the review of complex issues that require expertise beyond, or in addition to that available on the committee. The consultant does not take part in voting with the committee, or count toward quorum. Investigators and members of their research team are invited as guests to attend the IRB meeting. Such guests do not take part in committee deliberations or voting.

The IRB Chair and/or Administrator will meet with the Vice President for Academic Affairs at least once each academic year. All records of the IRB will be kept electronically and archived in a designated office. This will be the responsibility of the Office of Graduate Academic Affairs.

Before a research project involving human subjects is initiated, it must first be reviewed and approved by the IRB, and then conducted according to the procedures and guidelines set forth in this document, which are consistent with Federal and State regulations governing research. This includes all research involving human subjects, including but not limited to drug studies, diagnostic studies (invasive or non-invasive), *in vitro* studies utilizing clinical specimens, retrospective or prospective chart review, certain quality assurance activities, observational studies, surveys, and behavioral studies regardless of whether or not the research is funded by an outside agency. Research involving the use of existing data must be approved prior to the initiation of the protocol used to analyze the data. This is considered a retrospective study, and while there are no clinical procedures involved, the use of identifiable data previously collected from human subjects is considered research and must be approved by the IRB prior to the data analysis.

The MC IRB also provides IRB services to community professionals who are alumni and conducting research in nearby facilities (e.g. private practices). This service is made available to community professionals on a case-by-case basis and the IRB does not charge for all such applications. The IRB process will be independent of any existing professional-University relationship. The IRB will determine whether or not providing such review for a particular researcher poses a conflict of interest. If a conflict of interest is identified, steps will be taken to eliminate or manage the conflict.

The IRB may request documentation of IRB approval or determination of exempt status from other sites for collaborative studies.

The IRB Chair or designee has the authority to act on behalf of the IRB when immediate action is required prior to a convened IRB meeting to protect therights and welfare of human subjects. The IRB Chair or designee, in conjunction with IRB Administrator (if necessary) has the authority to evaluate and provide a resolution for emergent issues related to human subject protections that are not covered by these policies. Any such action will be brought to the attention of the convened IRB at the next meeting. The IRB also has the authority to promulgate or amend policies and procedures as necessary for the proper protection of human subjects in research.

Investigators bear the primary responsibility for ensuring that research protocols meet the standards established by both Federal and State regulation and the Institutional Review Board. Compliance with these regulations helps to ensure the protection of human subjects and the integrity of MC as a research institution.

Policies, guidance, procedures and information related to the conduct of research are presented in this document as a resource and guide to educate investigators on the issues governing human subject research, as well as to assist them in the process for submitting their research protocols to the IRB. The Office of the IRB may be contacted at 516-323-3380.

Federal Regulations referred to throughout these policies and procedures are as follows:

45 CFR 46 (i.e. Title 45 Code of Federal Regulations Part 46: Protection of Human Subjects), hereafter referred to as the Common Rule, which applies to research involving human subjects conducted by the Department of Health and Human Services (DHHS) or supported in whole or in part by DHHS.

21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards), which apply to all research involving products regulated by the Food and Drug Administration (FDA), including research and marketing permits for

drugs, biological products, or mechanical devices for human use, food and color additives, or electronic products. Federal funds do not need to be involved.

45 CFR 160 and 164 (Health Insurance Portability and Accountability Act)

It is the policy of MC that the same standards shall apply to all research, regardless of the funding source. When research involves products regulated by the FDA, both DHHS and FDA regulations apply, and the requirements of both sets of regulations must be met.

Distinction Between Research and Standard Practice

The Belmont Report defines the Ethical Principles and Guidelines for the Protection of Human Subjects of Research and is commonly accepted as the standard by which all research involving human subjects should be conducted. The MC IRB has assured the Office for Human Research Protections that they will comply with the ethical principles put forth in the Belmont Report. One of the areas specifically addressed in the Belmont Report is the boundary between clinical care and research, and the following excerpt provides a distinction between the two:

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

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

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental", in the sense of new, untested or different, does not

automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

*Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects". (*The Belmont Report, Office of the Secretary*: "Ethical Principles and Guidelines for the Protection of Human Subjects of Research".* The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18,1979)

MOLLOY UNIVERSITY IRB MANUAL
Policy 1: IRB Review and Approval: Categories of Review

The IRB shall review all research involving human subjects, require modification where necessary, and approve or disapprove as appropriate. The IRB will comply with federal regulations at 45 CFR 46.111 (DHHS) and 21 CFR 56.111 (FDA), institutional policies, state regulations (if required), and the terms of the Federal-Wide Assurance (FWA) between MC and DHHS in order to determine whether protections for human research subjects are adequate.

The IRB will utilize three review categories when considering research protocols. The IRB Chair or designee will determine the appropriate category of review based on the type of research to be conducted.

A. Exempt: Research reviewed by IRB Chair/designee but NOT subject to continuing review, according to criteria outlined in 45 CFR 46.104
B. Expedited: Research reviewed by IRB Chair/designee, not subject to continuing review under the 2018 requirements, unless FDA regulated or otherwise required by the IRB. [For expedited review, the IRB Chair/designee shall have the same authority as the IRB except they may not disapprove the research]
C. Full Board: Research reviewed by full IRB committee, subject to continuing review [A research activity may be disapproved only after full board review].

Continuing review, protocol amendments, consent form modifications, adverse event reports, protocol violations, and other related research activities will be reviewed by expedited or full board review procedures as appropriate, using criteria at 45 CFR 46.110 and 21 CFR 56.110.

Studies approved via the Exempt or Expedited process that are not subject to formal continuing review may be subject to an internal annual reporting process.

1.1 Exempt Research Categories

Research activities qualify for exemption status (i.e. exemption from committee member review and continuing review) as long as the activity fits into one of the categories below and the activity involves no foreseeable risk to human subjects. This category does involve review of research by IRB staff and the IRB Chair/designee, but studies deemed “exempt” are not subject to continuing review. Criteria used to determine if a research protocol qualifies for this review are found at 45 CFR 46.104. Final determination of exempt status will be made by the IRB Chair or designee.

Note: Research involving prisoners is not eligible for exempt review except for research aimed at involving a broader subject population that only incidentally includes prisoners. There are also limitations on the applicability of Exempt Category 2 for research involving children.

The following categories of research will generally qualify as

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes:

- Research on regular and special education instructional strategies; and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

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

- Information obtained is recorded in such a manner that the identity of the **human subjects cannot be readily ascertained, directly or through identifiers linked to the subjects; or**
- Any disclosure of the human subjects' responses outside the research would not reasonably place the **subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation; or**
- The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

Note: The exemption for research involving survey or interview procedures or observation of public behavior does not apply to research involving minors (17 years old or younger), EXCEPT for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including

data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

- The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Any disclosure of the human subjects' responses outside the research would not reasonably place the subject at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
- The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

- The identifiable private information or identifiable biospecimens are publicly available;
- Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot be readily ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
- The research involves only information collection and analysis involving investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 165.512(b); or
- The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research is subject to additional privacy requirements outlined in 45 CFR 46.104

5. Research and demonstration projects that are conducted or supported by a

department or agency, or otherwise subject to the approval of department or agency heads, and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies

a. Wholesome foods without additives are consumed or
b. Food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service to the U.S. Department of Agriculture.

Criteria used to determine if a research project qualifies as exempt from continuing review may be found at 45 CFR 46.104. Final determination of exempt status will be made by the staff of the IRB in conjunction with the IRB Chair or designee. The IRB will receive a report at each meeting of all applications that have been reviewed and approved using the exempt review procedure bi-annually.

Exempt Review Procedure

Refer to Policy 2 for directions on how to submit a protocol for exempt review. If an investigator determines that his/her proposed research activity falls into one of the exemption categories, s/he can complete the ***Application for Exempt Review***. The IRB Chair will review this application to determine whether or not the research activity qualifies for exemption. The Chair will then notify the investigator in writing regarding the status of the application.
Notification will indicate that the application was fully approved or that it requires modification/clarifications in order to secure approval. The letter will cite the specific category under which the research qualifies as exempt, and will be signed by the IRB Chair/designee or IRB Administrator. Approval is valid as long as the project continues as stated in the original proposal. No changes that might affect the categorization of the research as exempt may be implemented until first reviewed and approved by the IRB Chair/designee or IRB Administrator.

If the Chair determines that the protocol does not qualify as exempt, the investigator will be advised in writing to submit the protocol to the IRB for either expedited or full board review.

Note: Exempt studies are held to the same ethical standard as any other research study. The exemption status does not absolve the investigator from following regulatory and ethical guidelines for research at MC or any of the facilities that utilize the MC IRB.

1.2 Expedited Research Categories

The IRB may use the expedited review procedure to review research activities that:

- Involve only procedures listed in one or more of the categories allowed by DHHS as listed below

  If, the IRB reviewer determines the study is not minimal risk despite falling into one of the expedited review categories, additional rationale would need to be provided to justify a higher level of review.

The categories in this list apply regardless of the age of subjects, except as noted. The expedited review procedure is not permitted when identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

Categories (1) through (7) below pertain to both initial and continuing review. The IRB can review minor changes to research approved by the full committee via the expedited review procedure. A minor change is defined as one that has no substantive effect upon or reduces the protocol risk already approved by the full committee.

Categories

1. Clinical studies of drugs and medical devices only when the following conditions are met.

- Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- Research on medical devices for which an investigational device exemption application (21 CFR Part 812) is not required, OR the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

    - from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; OR
    - from other adults and children (persons under 18 years old), considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

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

    - Hair and nail clippings in a non-disfiguring manner;
    - Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
    - Permanent teeth if routine patient care indicates a need for extraction;
    - Excreta and external secretions (including sweat);
    - Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;
    - Placenta removed at delivery;
    - Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
    - Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
    - Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
    - Sputum collected after saline mist nebulization.

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

Examples

- Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
- Weighing or testing sensory acuity;
- Magnetic resonance imaging;
- Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
- Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may qualify as exempt. This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may qualify as exempt. This listing refers only to research that is not exempt.)
8. Continuing review of research previously approved by the convened IRB as follows:
    a. Where:

    - the research is permanently closed to the enrollment of new subjects;
    - all subjects have completed all research-related interventions; and
    - the research remains active only for long-term follow-up of subjects; or

(b) where no subjects have been enrolled and no additional risks have been identified; OR

(c) where the remaining research activities are limited to data

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories

two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

NOTE: These categories have been provided by DHHS as areas of research that involve minimal risk and qualify for expedited review. Although a specific research activity may fall within one of these categories, it may be determined by the expedited reviewer that the research is greater than minimal risk and therefore referred to full board review. Rationale would need to be provided as to why the research is not minimal risk. The standard requirements for informed consent (or its waiver, alteration, or exception) apply to studies approved via expedited review.

Research submitted for expedited review is not subject to meeting deadline dates. Protocols are reviewed as they are submitted by the IRB Chair or a designee. The term "expedited" refers to the type of review mechanism that is employed and does not necessarily mean "quicker". A minimum of 3 weeks is expected for expedited initial review.

Expedited Review Procedure

Refer to Policy 2 for directions on how to submit a protocol for expedited review. Once IRB Chair determines that a research application meets all criteria for expedited review (e.g. applicability to one of the categories referenced above), the application materials are sent to a Chair or designee with the appropriate expertise, chosen from the members of the IRB. The full protocol, including the consent form and all pertinent source material, will be considered. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewer(s) may not disapprove the research (disapproval may only be decided at a meeting of the full committee). When a protocol is approved through expedited review the specific permissible category under which it qualifies will be cited in the approval letter and the IRB meeting minutes.

Once the review has been completed, the investigator will be notified regarding the status of the application. This written notification will indicate that the application was either fully approved, requires modification/clarifications in order to secure approval, or tabled [protocol does not qualify for expedited review or substantive issues regarding the protocol and/or consent must be addressed]. An approval period will be determined. The principal investigator is required to submit annual report materials in sufficient time to avoid any lapse between in required IRB oversight.

The IRB receives and notes a report at the IRB meeting of all applications that have been reviewed and approved using the expedited review procedure, or determined to be exempt.

NOTE: A protocol is not approved until <u>all</u> required modifications are received and approved by the IRB. There may be **no activity** on the project until these modifications have been approved by the IRB, and the approval letter has been received by the PI indicating approval and permission to begin the study. The term of the approval will be indicated, as well as the date that the first report or renewal is due. Any special conditions that have been applied to the research will also be indicated in the approval letter. The appropriate person by whom changes will be reviewed will be named (i.e. IRB Chair, IRB Administrator, Chair designee, etc.) depending on the nature of the items to be submitted. Each protocol will receive an IRB Protocol Number.

<u>Limited IRB Review</u>

The IRB may utilize the expedited review procedure to review research for which limited IRB review is a condition of exemption under 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (d)(8).

IRB determinations for exempt studies requiring limited IRB review will consist of a designated IRB reviewer's written concurrence in the IRB file that the research described in the application satisfies one or more of the eligible categories of exempt research requiring limited IRB review.

If the designated IRB reviewer requests modifications to any of the materials submitted, a final determination will not be provided unless and until such modifications have been returned to a designated IRB reviewer for review.

Projects requiring limited IRB review that are determined to meet criteria for exemption will be included in the agenda and minutes of a subsequent convened meeting of the IRB. The IRB members will be given the opportunity to review or comment on any such project.

1.3 Full Review Category

All other research (i.e. non-exempt, non-expedited) will be reviewed by the IRB at a convened meeting. Full board review refers to review at a convened IRB committee meeting where a minimum of 5 members are present and a quorum vote is obtained by 3 members of the voting membership including at least one member whose primary concerns are in non-scientific areas). Approval of research is by a

majority vote of the quorum. Should the quorum fail during a meeting (e.g. loss of a majority through recusal of members with conflicting interests, early departures, or absence of a non-scientific member) the IRB may not take further actions or votes unless a quorum is restored.

Copies of all protocols to be reviewed at the meeting are distributed to the members approximately 7 days before the meeting. The entire committee receives the full protocol, including the consent form, all pertinent source material, and all required IRB forms. Each protocol is typically assigned to primary and secondary reviewers who present the protocol and begin the committee deliberations. Reviewers are selected according to the specific expertise needed to review the protocol properly. Primary and secondary reviewers review entire submission. In addition to scientific expertise, consideration will be given to special issues and populations when reviewers are assigned whenever possible. When appropriate expertise required for review of a particular protocol is not available among the IRB members, a consultant reviewer may be called in when needed.

After the meeting, the investigator is notified in writing regarding the status of the application. The application may be granted **Approval** (approved as submitted with no modifications required), **Contingent Approval** (protocol requires directed revisions (modifications) that do not affect the safety of the research subject and are clearly delineated -the IRB Chair/designee may approve the study once the directed changes are made and submitted), **Tabled** (substantive issues regarding the protocol and/or consent form must be addressed – the investigator response must be reviewed by the IRB at a convened meeting) or **Disapproval** (the IRB has serious concerns about the study and finds it not eligible for approval). The approval period will be indicated in the letter, and the approved consent form will be stamped (copies of which must be utilized for consenting subjects).

According to federal regulations, approval periods may not exceed one year. Approval periods of projects requiring full board review (initial or continuing) are dependent on the degree of risk associated with a study, and cannot extend beyond the 1 year anniversary (minus 1 day) of the convened committee review date. The date of approval will be the date of the convened IRB meeting where a determination was made (approval or contingent approval). For example, if a study was reviewed by the full committee on June 20, 2007, the expiration date will be no later than June 19, 2008 no matter when the final approval date might be (which might be a later date if modifications/clarifications were required), since it is dependent on the date of the meeting and not the date that the conditions of approval were met.

1.4 Review more often than

Unless specifically waived by the IRB, research that meets any of the following criteria will require review more often than annually:

- Significant risk to research subjects (e.g. death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
- The involvement of especially vulnerable populations likely to be subject to coercion ;
- A history of serious or continuing non-compliance on the part of the PI.

The following factors will also be considered when determining which studies require review more frequently than on an annual basis:

- The probability and magnitude of anticipated risks to subjects.
- The likely medical condition of the proposed subjects.
- The overall qualifications of the PI and other members of the research team.
- The specific experience of the principal investigator and other members of the research team in conducting similar research.
- The nature and frequency of adverse events observed in similar research at this and other institutions.
- The novelty of the research making unanticipated adverse events more likely.
- Any other factors the IRB deems relevant

1.5 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research

The IRB will determine the need for verification from outside sources on a case- by-case basis and according to the following criteria:

- Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.

- Protocols conducted by Principal Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.

- Protocols randomly selected for internal

- Whenever else the IRB deems verification from outside sources is relevant

The following factors will also be considered when determining which studies require independent verification:

- The probability and magnitude of anticipated risks to subjects.
- The likely medical condition of the proposed subjects.
- The probable nature and frequency of changes that may ordinarily be expected in the type of research to be proposed.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments and/or adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

1.6 The Appeal Process

A PI may appeal a decision made by the IRB within 120 days of the date of the decision letter from the IRB. The appeal must be made in writing and sent to the IRB Chair or Office of the IRB along with any supporting materials. The Chair and Office of the IRB will review the appeal and decide whether additional information is necessary to present at the IRB meeting. The appeal will be brought to the next convened meeting of the IRB. The Chair may invite the PI to attend the meeting to give a presentation of the protocol and to address problematic issues. Written notification of the IRB's decision of the appeal will be sent to the PI following the meeting.

A decision for disapproval after appeal is final. If significant modifications are made to a previously disapproved protocol it may be submitted as a new protocol. The IRB Chair has the authority to determine whether a previously disapproved protocol has been amended sufficiently to warrant review as a new protocol.

Policy 2: How to Submit a Protocol to the IRB

Research activities that involve human subjects, as described in Policy 1, must be submitted to the IRB and must be approved prior to commencement of any research activity. The following is a description of the IRB application forms that are required. The forms required will depend on the category for which the research activity qualifies (exempt, expedited, or full-committee review) and the particular components of the study. [*See Policy 1 for a detailed description of these three review categories*]. Note that if the IRB determines that a different category is applicable than originally submitted, additional information may be required from the Principal Investigator. The IRB Office will provide assistance in determining which forms are required for a particular research activity. Forms are also provided for post-approval activity on research protocols, as detailed below.

In order for a protocol to be placed on the IRB meeting agenda, it shall be submitted on or before the deadline date (typically **14 days prior** to the scheduled meeting) and conform to all of the requirements. If the submission is incomplete, the IRB office shall notify the principal investigator (PI) of the deficiencies and/or return the submission to the PI.

Studies originating from another institution that will be conducted at a MC site must be reviewed by the MC IRB and have a designated local PI from MC if MC is only/primary research site. Students doing research must have a qualified mentor to oversee the conduct of the research. This includes all students. Mentor must be designated as the PI or co-investigator. There must be one PI who has overall responsibility for the study; all others are co-investigators or sub-investigators.

The MC IRB provides IRB services to other entities for which a Reliance Agreement has been executed. Studies that originate at these other entities are subject to the same requirements as MC.

In addition to the designation of a PI, all research protocols submitted for IRB review must list all key personnel involved in the conduct of the study as co-investigators; only those individuals so listed may recruit subjects and perform research-specific procedures, including obtaining informed consent. An investigator may not participate in research until he/she has complied with institutionally mandated researcher education. Based on current regulatory or site-specific requirements, the IRB may mandate additional education prior to an individual's involvement in research. Protocols involving more than one area of expertise must include co-investigators from the appropriate disciplines to ensure proper execution and oversight of the protocol.

IRB Submissions – Required Forms

For new protocols, one complete original packet (including all original signatures) must be submitted to the IRB Office. Exempt and Expedited applications are reviewed on a rolling basis. Applications for full board review must be submitted at least 14 days prior to the scheduled meeting.

Submission of amendments/progress reports/SAE's or any other item requiring IRB review for ongoing, approved studies will require one complete original with all original signatures, and any changes submitted in redlined edited review mode.

The IRB Office encourages all investigators to contact the IRB Office for assistance in preparing the IRB application forms. Please refer to the following chart for a complete listing of all IRB forms and guidance on which forms are required for Exempt, Expedited and Full Board review. Also listed are forms that are available for ongoing research studies (for amendments, renewals, etc.).

Step 1: Determine the appropriate review category (See Policy 1 or call the Office of the IRB for assistance)

Step 2: Complete the required IRB submission form as indicated in the table below for the applicable category.

Step 3: Assemble your submission packet, including all completed IRB submission form sections plus:

- Research protocol (the detailed plan describing the objectives, design, methodology, statistical considerations, etc. of the study)
- Data collection forms (if appropriate)
- Consent form (if applicable)
- Any other written information to be provided to subjects
- Investigator's brochure (if available)
- Any advertising or recruitment materials
- Survey and/or other research instruments

Step 4: Upload your submission package to IRBNet
https://www.irbnet.org/release/index.html

For assistance please contact
Patricia A. Eckardt, PhD, RN, FAAN
Chair, Molloy University Institutional Review Board
Professor, Barbara H. Hagan School of Nursing and Health Sciences
peckardt@molloy.edu
1-516-323-3711

Form Name	Exempt	Expedited	Full-Committee	Used for Approved Protocols
Full IRB Application Form	✓	✓	✓	
Note—The above form has sections for all IRB applications (exempt, expedited, and full). ***ALL APPLICATIONS*** *(EXEMPT, EXPEDITED and FULL)* ***MUST COMPLETE SECTION I: IDENTIFYING DATA Pages1-13.*** *Expedited and Full Review Applicants then complete Sections* II-XV *on pages 12-36. Exempt review applicants then complete Section XVI , pages 38-48(in addition to Section I)*	See note in Column 1 for sections to complete	See note in Column 1 for sections to complete	See note in Column 1 for sections to complete	N/A
IRB Form: Protocol	✓	✓	✓	
Informed Consent Guidance	Or consent scripted process	✓	✓	
Human Subjects' Research Data Protection Plan Guidance	✓	✓	✓	
Financial Disclosure/COI (if applicable)	✓	✓	✓	
HIPAA Form (if applicable)	✓	✓	✓	
FERPA Form (if applicable)	✓	✓	✓	
Below Forms are for Amendments and Annual Reports and Reviews				
Amendment to Approved Protocol				✓
Application for Ongoing/Continuing Review			✓	✓
Expedited and Exempt Research Protocol Annual Report Form	✓	✓		✓

Policy 3: Research and HIPAA (Health Insurance and Accountability Act) Privacy Rule Compliance

An individual's protected health information (PHI) may only be used for research after the investigator has obtained the approval of the IRB. Where the Privacy Rule, the Common Rule, and/or the FDA's human subject regulations are applicable, each set of requirements must be met. When there is a difference in the requirements, the highest level of protection shall be followed. The IRB shall serve as the Privacy Board for research.

The full text of the HIPAA regulations is available at http://www.hhs.gov/ocr/hipaa.

HIPAA stands for the Health Insurance Portability and Accountability Act. It is federal legislation designed to enable a person to go from one health insurance plan to another with continuity of care and to ensure that he/she will not be denied coverage for a "pre-existing condition" (portability); it details government oversight to protect fraud and finally adds protections for confidentiality of protected health information (PHI) that is collected (accountability).

Definitions:

Authorization: An individual's signed permission that allows a covered entity to use or disclose the individual's PHI for the purpose(s), and to the recipient(s), as stated in the Authorization.

Covered entity: A facility that conducts health care operations involving the creation and transmission of protected health information or PHI. MC is not a covered entity.

Disclosure: The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Member of the workforce of the covered entity: An individual who is employed or credentialed or holds privileges at a specific entity.

Privacy Rule: A federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that protects certain individually identifiable health information.

Research Privacy Board: A group of individuals responsible for the review and approval of requests for the disclosure of PHI for research purposes.

Research Privacy Officer: A person designated by the covered entity to oversee HIPAA compliance specific to research. Responsibilities include handling patients' privacy complaints, and training and auditing for HIPAA compliance.

Use: With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity that maintain such information.

3.1 Protected Health Information

Protected health information (PHI) is individually identifiable health information that is collected for treatment, diagnosis or research purposes. HIPAA details eighteen items that render PHI identifiable:

1. Names
2. Geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code in certain situations.
3. All elements of date (except year) for dates directly related to an individual, including birth date, discharge data, date of death; and all ages over 89 and all elements of dates indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers
13. Medical Device Identifiers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code.

Research Categories Under HIPAA

There are three categories of research data to be considered under

1. Identifiable information (to which the rule applies)

2. De-identified information (to which the rule **does not apply**)
3. Limited data set (a middle option, to which limited parts of the rule apply)

De-identified Information

PHI that is stripped of all of the eighteen identifiers listed above is considered de-identified and is not subject to requirements under HIPAA. PHI can be de-identified for research purposes by removing the 18 identifiers and using a linked code (not derived from any identifying information, i.e., initials), to which access is extremely limited and well protected.
Databases containing identifiable PHI used for research purposes are subject to restrictions under HIPAA.

Limited Data Set

A limited data set (used in conjunction with a data use agreement) refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, without obtaining either an individual's authorization or a waiver (or an alteration) of authorization for its use and disclosure.

The following identifiers **must be removed** from health information if the data are to qualify as a limited data set:

1. Names
2. Postal address information, other than town or city, state and ZIP code
3. Telephone numbers
4. Fax Numbers
5. E-mail addresses
6. Social Security Numbers
7. Medical Record Numbers
8. Account Numbers
9. Certification/license numbers
10. Device identifiers and serial numbers
11. Vehicle identifiers and serial numbers including license plate numbers
12. Web universal resource locators (URLs)
13. Internet protocol (IP) address numbers
14. Biometric identifiers, including fingerprints and voiceprints
15. Full-face photographic images and any comparable images
16. Health plan beneficiary numbers

Only the following identifiers may be used in a limited data

- Dates
- Geographic information (except for street address)
- Other unique identifying numbers, characteristics, or codes that are not expressly excluded

When a limited data set is used, there is no requirement to track disclosures. The minimum necessary standard does apply (see below). The recipient of the limited data set must sign a data use agreement.

Data Use Agreement
A data use agreement is an agreement into which the covered entity enters with the intended recipient of a limited data set that generally describes the permitted uses and disclosures of the PHI in a limited data set and how the data will be protected.

If an investigator plans to use a limited data set for research, he/she must submit a data use agreement with his/her IRB protocol submission. See Policy 2: How to Submit a Protocol to the IRB for guidance.

Minimum Necessary Standard
HIPAA also requires that researchers comply with a "minimum necessary standard". This means that a research protocol must limit the PHI it uses, discloses, or requests to the minimum necessary to achieve that purpose. The standard applies to all research involving the use of PHI, including protocols involving the use of a limited data set and/or a waiver of authorization, and for reviews preparatory to research.

3.2 Authorization from the Research Subject

Authorization is a person's signed permission allowing a covered entity to use or disclose that person's PHI as specified in the authorization form. There are important differences between Privacy Rule requirements for individual authorization, and Common Rule and FDA requirements for informed consent (see Policy 5 – Informed Consent). HIPAA requires more specific details about all possible uses and disclosures of PHI ("use" refers to the sharing of PHI within the covered entity, "disclosure" refers to the sharing of PHI outside the covered entity). The information required under HIPAA for authorization may be incorporated into the research consent form. Therefore a subject may provide consent and authorization together as part of the informed consent process, if determined by the IRB to be appropriate.

The following items must be detailed in an

- The PHI that will be used or disclosed
- The people/organizations who will use or disclose the PHI
- The people/organizations who will receive the PHI
- The purpose of the use or disclosure
- An expiration date or event for the use or disclosure of the

- The right to refuse to provide the authorization (which would exclude the individual from participating in the research)
- The right to revoke authorization including the procedure for doing so (in writing).
- The research subject's dated signature
- The investigator's obligation to provide a signed copy of the authorization to the subject
- The PHI may no longer be protected by the Privacy Rule once it is disclosed by the covered entity

Individual Rights

Under HIPAA, individuals have the right to:

- **Access their PHI:** The individual may request a copy or the opportunity to inspect the PHI that has been utilized as part of the research study. This access is limited to a "designated record set" which includes PHI that is used to make clinical or billing decisions about a subject. In order to prevent the compromise of research data, access can be postponed until the research is complete, as long as this is clearly explained in the authorization (or research consent form).
- **Request amendment to their PHI:** The individual has the right to request an amendment to their PHI. The institution will determine whether or not the request is appropriate.
- **Receive a record of certain disclosures of their PHI made within the previous 6 years:** This does not apply to disclosures that were made pursuant to an authorization, or disclosure of a limited data set. Individuals may request a record of disclosures made under a waiver of authorization or disclosures required by law and for public health purposes. Therefore, any such disclosures must be tracked. (See Tracking Disclosures).
- **Request restrictions on uses and disclosures:** Individuals can request certain restrictions on uses and/or disclosures of their PHI, if it is determined that the request is appropriate and feasible.
- **Request receipt of communication of their PHI by alternative means/location:** An individual may request, for example, that a different address be used to communicate information (home vs. work). Reasonable request must be accommodated, and the individual does not have to explain the basis for the request.
- **Revoke their authorization:** A revocation of authorization must be made in writing. If research authorization is revoked, PHI may no longer be used or disclosed, except to the extent that the PHI has already been included in study analyses, or if the use or disclosure is needed to maintain the integrity of the research study (i.e. account for withdrawal, report adverse event, etc.).

Note: Because New York State Law does not distinguish between living and deceased individuals in their definition of human subject, the same privacy rule standards shall apply to the use of decedent PHI.

3.3 Waiver of Authorization

There are situations in which the IRB can waive the requirement that subjects sign an authorization form. In general, a Waiver of Authorization could be granted under similar circumstances that the IRB grants a Waiver of Informed Consent (e.g., for retrospective chart reviews, etc.).

Any study granted a waiver of informed consent and approved by the IRB on or **after April 14, 2003**, must also have a Waiver of Authorization. Any study approved with a Waiver of Informed Consent **before April 14, 2003**, does not need a Waiver of Authorization.

Note: A Waiver of Authorization does **not mean the research is exempt from HIPAA privacy rules**. It only means the investigator does not need to obtain signed authorization from each research subject.

In order to qualify for a Waiver of Authorization, an investigator must represent the following:

- The use of PHI for research does not represent more than a minimal risk to privacy
- The research could not be done without the requested PHI.
- It would not be practical to obtain signed authorization from research subjects.
- The specific elements of the requested health information are not more than the minimum necessary to conduct the study.

Partial Waiver of Authorization

There are circumstances that would require a PI to obtain a partial waiver (or alteration) of authorization. See Reviews Preparatory to Research below and Policy 4: Recruitment by the Researcher.

Tracking Disclosures

All disclosures (release outside the covered entity) of PHI made without the written authorization of the research subject must be tracked. This includes studies conducted under a waiver of authorization, as well as situations where consent/authorization was obtained but the recipient of the PHI is not listed on the consent/authorization form.

Note: When a limited data set is used, there is no requirement to track disclosures.

The information that should be tracked includes:

- Date of disclosure
- Name of the person/entity who received it and their address (if known)
- A brief description of the disclosed PHI
- A brief statement of the purpose of the disclosure.

A modified tracking mechanism is available for research involving the disclosure of PHI from 50 or more subjects (i.e. during epidemiological research). Under a modified tracking mechanism, the researcher must be prepared to provide:

- The name and description of all protocols involving disclosure of 50 or more subjects
- A brief description of the types of PHI disclosed
- The dates or time periods of the disclosures
- Contact information of the recipients
- A statement that a specific individual's PHI may or may not have been disclosed for a particular study.

3.4 FERPA Family Educational Rights and Privacy Act

Protecting the Privacy of Student Education Records
Student education records are official and confidential documents protected by one of the nation's strongest privacy protection laws, the Family Educational Rights and Privacy Act (FERPA). FERPA, also known as the Buckley Amendment, defines education records as all records that schools or education agencies maintain about students.
FERPA gives parents (as well as students in postsecondary schools) the right to review and confirm the accuracy of education records. This and other United States "privacy" laws ensure that information about citizens collected by schools and government agencies can be released only for specific and legally defined purposes. Since enacting FERPA in 1974, Congress has strengthened privacy safeguards of education records through this law, refining and clarifying family rights and agency responsibilities to protect those rights.
FERPA's legal statute citation can be found in the U.S. Code (20 USC 1232g), which incorporates all amendments to FERPA. FERPA regulations are found in the Federal Register (34 CFR Part 99). FERPA's 1994 amendments are found in Public Law (P.L.) 103-382.

FERPA Restricts Disclosure of Student Records

Local education agencies and schools may release information from students' education records with the prior written consent of parents, under limited conditions specified by law, or as stated in local agencies' student records policies. The same rules restricting disclosures apply to records maintained by third parties acting on behalf of schools, such as state and local education agencies, intermediate administrative units, researchers, psychologists, or medical practitioners who work for or are under contract to schools.

If an education agency or a school district has a policy of disclosing records, it must specify the criteria for determining school officials within an agency, including teachers, who have a legitimate educational interest. Generally, school officials have legitimate educational interest if they need to review an education record to fulfill their professional responsibilities.

Teachers and school officials who work with the students and schools to which students apply for entrance may also have access to education records without prior consent of the parent. In addition, information from students' records may be released to state and local education officials to conduct audits or to review records in compliance with Federal laws. Schools may also disclose information from education records without the consent of parents in response to subpoenas or court orders. A school official must make a reasonable effort to notify the parent before complying with the subpoena unless the subpoena is issued to enforce a law and specifies not to notify the parent. In emergencies, school officials can provide information from education records to protect the health or safety of the student or others.

There are cases when schools or school systems decide it is in the public interest to participate in policy evaluations or research studies. If student records are to be released for these purposes, the school or school system must obtain prior consent of the parent. Signed and dated written consent must:

- Specify the records that will be released;
- State the reason for releasing the records;
- Identify the groups or individuals who will receive the records.

In general, information about each request for records access and each disclosure of information from an education record must be maintained as part of the record until the school or agency destroys the education record. Outside parties receiving records must receive a written explanation of the restrictions on the re-release of information.

Additional FERPA Provisions

In 1994, the Improving America's Schools Act amended several components of FERPA, tightening privacy assurances for students and families. The amendments apply to the following key areas:

- Parents have the right to review the education records of their children maintained by state education agencies;
- Any third party that inappropriately re-releases personally identifiable information from an education record cannot have access to education records for five years;
- Information about disciplinary actions taken against students may be shared, without prior consent of the parent, with officials in other education institutions;
- Schools may release records in compliance with certain law enforcement judicial orders and subpoenas without notifying parents.

Policy 4: Recruitment of Study Subjects

Investigators must include their plan for recruiting human research participants in their IRB application. If a protocol is already approved and an investigator wishes to utilize a new method for recruiting participants, the recruitment plan must first be approved by the IRB.

Potential research participants may be recruited for research studies using a number of different methods. Potential recruitment methods include direct contact, advertising, record review, database review, or other written/verbal correspondence. Recruitment methods must comply with federal regulations governing the protection of human subjects, as described below, as well at Institutional policies, HIPAA, and FERPA Privacy Rule requirements.

4.1 Recruitment Mechanisms

Potential subjects may be recruited by either of the following mechanisms. The mechanism for recruitment must be described by the PI in the protocol and submitted to the IRB for approval before implementation.

1. **Recruitment by Clinician or Treatment Staff**

Acceptable Methods:

a. A clinician, **who is also a researcher**, may approach a patient he/she is treating about participating in any IRB approved study for which that clinician is conducting research. The clinician's treatment personnel (who already have access to a patient's identifiable health information by virtue of the treatment relationship) may also approach the patient about participating in research. The clinician and the treatment staff must note any such communication in the patient's medical record.

Note: Direct recruitment for a study by a clinician/researcher or his/her treatment staff is not restricted by HIPAA. These personnel already have a reason to know the patient's PHI and, assuming the study (and the recruitment process) has been approved by the IRB, these personnel may approach the patient about participating in the study without additional HIPAA authorization. Subsequent authorization may be required once the individual is enrolled into the study in order to collect and use additional PHI for research.

b. A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may approach a patient about participating in another researcher's study. The clinician or staff must note such communication in the patient's medical record. If the patient agrees to be referred to the researcher, the following language is suggested:
I discussed the possibility of referring the patient to *[doctor or team] for [describe research*

*study]. **The patient agreed to the referral, and to sharing information about his/her condition with the researcher**.*

c. A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may give the patient another researcher's name and contact information. The patient may then choose to contact that researcher directly.

d. A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may discuss a patient's eligibility with the research personnel as long as all information about the patient has been de-identified. If the research personnel think the de-identified patient would be eligible for the study, the treatment personnel could then obtain the patient's permission to give the research personnel the patient' name or give the patient the researcher's contact information (see b and c above).

e. A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may send a letter to the patient about how to join an IRB approved study as long as the content of the letter is approved by the IRB.

Note: Unless the IRB approves a waiver of authorization for study recruitment purposes, the letter may NOT be co-signed by the researcher and the researcher may not have a copy of the letter with the patient's name on it.

2. Recruitment by the Researcher

If the treating clinician's direct approach to the patient or the patient's prior authorization is impracticable, the researcher may ask the IRB to grant a partial waiver of the patient's authorization for recruitment purposes.

A partial waiver of authorization may be requested for the

a) To allow treatment staff to refer patients to the researcher or to share PHI with the researcher without first speaking to the patient about the referral.

b) To advertise about the study and screen by phone potential subjects for the study.

4.2 Recruitment Methods

Potential subjects may be recruited for research studies using a variety of methods, including direct contact (where appropriate), advertising, chart reviews, database review, or other written/verbal correspondence. All of these methods must be consistent with federal regulations regarding the rights and welfare of

potential subjects (Common Rule Requirements), the Privacy rule (HIPAA Privacy Rule Requirements), and Institutional policies.

4.2.1 Recruitment through Chart Reviews

Investigators may use existing records, or other private information, including databases, that they would normally have legitimate access to as part of their practice in order to identify potential research subjects.

An investigator may need to review records to which he/she does not have legitimate access in order to identify potential research subjects. Since this activity involves the use of PHI, a waiver of authorization must be obtained from the Privacy Board (see Policy 3 – HIPAA and FERPA).

4.2.2 Using Letters to Contact Potential Research Participants

In most cases, contacting potential research subjects by letter will occur only when that subject is familiar with the person writing the letter. If personal information about the subject is necessary in order to identify them as a potential participant (such as having a certain disease or clinical condition) then the contact shall come from a person that they would expect to have that information about them (e.g. their physician, a disease-related organization to which they belong, etc.).

Any letter that is sent to a potential research participant is subject to the same requirements as advertising, and must contain no coercive language. The letter should briefly explain the study, its purpose, and the reason why the person is being asked to participate. There should be a mechanism by which the person can express an interest (by calling their physician or a researcher, sending back a card, etc.). Failure to respond should never be construed as a willingness to participate. It should be clearly stated if a follow-up phone call is to come from the person who wrote the letter. It must also be clearly stated that participation is voluntary, and the subject has the right to refuse to participate without any loss of benefit to which he/she would otherwise be entitled. If possible, a consent form should be included, and a phone number where the person can direct questions about the study should be provided.

4.2.3 Optional Authorization for Research

Use of an Optional Authorization for Research Contact form must first be approved by the IRB. **Contact IRB Chair to access and discuss this form.**

By signing the Optional Authorization for Research Contact form, a potential subject, or his/her LAR, agrees to allow his/her name, date of birth, address, telephone number, and diagnosis to be shared with researchers. After receipt of the signed authorization, the researcher may contact the potential subject to discuss possible participation in a research study. If a potential subject agrees to be in the study, he/she must go through the process of informed consent (documented by a consent form), specific to that study.

The patient or his/her LAR must be given a copy of the signed Optional Authorization for Research Contact form. A copy of the signed form must also be kept in the patient's record at his/her doctor's office and in the study's critical documents at the researcher's office.

4.2.4 Advertising

No advertising material may be used prior to approval by the IRB. The IRB shall review all printed media advertisements, internet advertisements (which include more information than simply a listing of available trials), scripts of radio and television commercials, flyers, postcards, letters, pamphlets, brochures, videos, and any other advertising material proposed for use in recruiting study subjects.

The principal investigator must submit all advertising materials with the initial application or as an amendment to a previously approved study. The IRB will employ the appropriate review mechanism (i.e. full board or expedited) to review the advertising material based on its content. When reviewing, the IRB will assure that the advertising material:

- Is not unduly coercive (especially when targeted toward subjects who might be vulnerable to undue influence).
- Does not state or imply a certainty of favorable outcome or other benefits beyond that which is outlined in the consent form or protocol.
- Utilizes an appropriate typeface and visual effects.
- Includes appropriate wording and presentation (especially for audio and video presentations).
- Does not provide misleading information to potential subjects.

- Avoids portraying study procedures as “new”, and does not use phrases like “receive new treatment” that might lead study subjects to think they are receiving a modality or treatment of proven worth.
- Avoid use of the term “free treatment” when what is meant is that the study will not cost the subject anything.
- Provides payment information in a manner that does not emphasize the payment amount by use of a larger or bolder type.

Consistent with federal guidance in this area (FDA Information Sheets, 1998), the IRB limits the information that can be included in an advertisement to information that the prospective subject needs to determine their eligibility and interest.

When appropriately worded, the following items may be included in advertisements (if appropriate):

1. The name and address of the principal investigator, department and/or location of the research facility;
2. The condition or area under study and/or the purpose of the research;
3. In summary form, the criteria that will be used to determine eligibility for the study;
4. A brief list of participation benefits;
5. The time or other commitment required of the subjects; and
6. The location of the research and the person or office to contact for further information.

Note: No “open reads” for radio or television are permitted. Open reads are live discussions by a person on radio or television that are intended as advertisements. For example, when a radio host talks about how great a particular store is, and you are led to believe that it is their personal opinion when, in fact, they are reading or acting out an advertising script.

4.2.5 Recruitment of MC Employees and Students as Research Subjects

The use of employees and students as research subjects may be permitted depending on the nature of the research and as long as they are treated as any other research subjects would be in compliance with federal, state, and institutional policy regarding the use of human subjects in research. In most cases, investigators will not be allowed to recruit employees who work directly under their supervision. The final decision to allow employees as subjects will be made by the IRB on a case-by-case basis.

Employees and students who wish to become involved as research participants are subject to the same protections as any other human subjects. This applies to all research activities, including when the person volunteers as a normal control.

A consent form (if applicable) must be signed by all subjects, there are no exceptions made for employees or students.

4.2.6 Recruitment Incentives and Conflict of

Investigators and other members of the study staff (study coordinators, research assistants, etc.) shall **NOT** accept monetary or other bonuses as incentives to recruit or refer patients to research studies. Examples of such bonuses include but are not limited to payments for rapid recruitment, extravagant gifts such as computer or other office equipment, expensive meals, books, etc. Such payments or incentives may lead to the appearance of inappropriate practices in an effort to increase enrollment for personal gain, and might compromise the integrity of the research.

It is against the policy of MC for an employee to solicit or accept gratuities from patients, their families or friends for any services provided by the employee during work hours, or for any member of the employee's immediate family to accept gifts, gratuities, or entertainment that might influence the employee's judgment or actions concerning business of MC. For employees involved in research, this includes any payment from study sponsors above and beyond payment that has been approved in the study budget. Budgets that include bonuses for recruitment or other activities are never allowed.

4.2.7 Payment to Research Subjects

It is the policy of the MC IRB to review and approve payments in the form of cash and non-cash compensation for time and expenses associated with research participation. Any payment or non-cash compensation to research subjects shall not be of such an amount as to be coercive or to present undue influence on the potential subject's decision to participate in the research.
Reimbursement for travel costs and time spent will be considered and approved by the IRB on a protocol -by-protocol basis related to the risk-benefit assessment of the study. Any reimbursements or gifts to research subjects shall be detailed in the consent form and shall always be prorated so that there is no bonus payment for remaining in a study. Payments to parents are not considered appropriate by the IRB; the IRB may approve reimbursement for travel related expenses at a reasonable rate on a case-by-case basis. Payment to minors will be considered on a case-by-case basis.

Note: The MC IRB carefully considers **payment to minors** who are subjects in a research study. It may be appropriate to offer a non-cash option to minors who are enrolled in a research study in order to provide acknowledgment of their participation that can be understood and appreciated by the minor. The IRB may suggest that payment to minor research subjects be made in the form of a gift certificate to an age-appropriate store (toy store, etc.), toys, stickers, etc.

Payment to research subjects for participation is not considered a benefit, it is a recruitment incentive. The amount and schedule of all payments must be presented to the IRB at the time of initial application. The IRB will review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence.

Timing of Payments

Credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Subjects should be paid in proportion to their time and inconvenience as a result of their participation. Payments should be equally distributed so as not to offer an undue incentive to finish the study (e.g. higher payments for study visits toward the end of the study).

Generally, a completion bonus is not acceptable as it may be coercive. The IRB may review such practice on a case-by-case basis and determine whether the amount paid as a bonus for completion is reasonable and does not unduly influence subjects to stay in the study.

Disclosure of Payments

All information concerning payment, including the amount and schedule, should be described in the informed consent document.

4.2.8 Recruitment on the Internet

Recruitment of research subjects via the internet is subject to the same guidelines as other written recruitment material and must be approved by the IRB before implementation. Recruitment plans will be reviewed and evaluated in accordance with the basic principles governing human subject protections.

Policy 5: Informed Consent

Informed consent is not a single event or a form to be signed, but an ongoing educational process that takes place between a researcher and a prospective subject.

An investigator may **NOT** involve a human being as a subject in a research study unless the investigator has obtained the approval of the IRB for that study. The legally effective informed consent of the subject or the subject's legally authorized representative shall be required, except when a waiver is granted under FDA and OHRP guidelines (as described below). All consent forms shall conform to 45 CFR 46.116, 21 CFR 50.20, and Institutional requirements.

The ethical principle of respect for persons (autonomy) is maintained by the process of informed consent from human subjects involved in research, and is a necessary process to help ensure that research is conducted in an ethical manner.

The informed consent process is a comprehensive discussion between the investigator and a prospective subject of the:

- nature of the research study,
- risks and the benefits,
- alternatives to research, and
- rights of a study subject.

Informed consent is not valid unless the person consenting understands the information provided. An investigator must ensure, to the best of his/her ability, that prospective subjects understand why the research is being done and why they are being asked to participate.

The following definitions clarify the difference between consent, assent, and permission:

Consent forms are used to consent subjects 18 years of age and older.
Permission may be given by parents of subjects 17 years or younger (since the subjects themselves cannot legally consent to being in the study).
Assent forms are used to obtain agreement from the minor subject (17 years or younger) to be in the study. The minimum age for requiring assent is typically 7 years old.

Guidelines for developing a written consent form are available on the IRB website. This document contains suggested wording for each required element as well as HIPAA-required wording and mandatory elements for MC consent document.

5.1 Federally Mandated Elements of Informed Consent

The following are the Common Rule guidelines regarding informed consent (45 CFR 46.116). In addition to following the criteria outlined below, the consent process must be performed in such a way that the rights of the individual research subjects are not violated. Consent must be sought under circumstances where the subject or the legally authorized representative is given enough time to consider whether or not to be in the study, and that minimize the possibility of coercion or undue influence. Information provided to the subject or representative must be written in simple language, so all aspects of the research (e.g. purpose, risks, benefits) are clearly stated and an informed decision can be made. The prospective subject or representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information, An assessment of capacity may be required by the IRB.

Informed consent must begin with a concise and focused presentation of they key information that is most likely to assist a prospective subject or representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. A table at the front of the consent form or paragraph format (for shorter consents) would meet this requirement.

Informed consent as whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or representatives understanding of the reasons why one might or might not want to participate. No exculpatory language can be used.

In seeking informed consent the following information must be provided to each subject:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others, which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of any treatment that might be advantageous to the subject.

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- A statement describing the Institution's policy on liability for research related injury
- 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.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to the subject and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- One of the following statements about any research that involves the collection of identifiable information or identifiable biospecimens:
    - A statement that identifiers may be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subjects or legally authorized representative, if this might be a possibility; or
    - A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Note: In addition to the Common Rule requirements for informed consent, **HIPAA** requires specific details regarding use and disclosure of PHI which may be incorporated into the informed consent process and consent form. See Policy 3: Authorization from the Research Subject for guidance.

5.2 Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information must also be provided to each subject:

- 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 or father a child) which are currently unforeseeable.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue to participate will be provided to the subject.
- The approximate number of subjects involved in the study.

- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing
- If a study sponsor agrees to reimburse for research-related injury, such a statement should be added following the University's standard policy for such.
- Such other information which the IRB recommends as meaningfully adding to the rights and protection of subjects.
- If the research is FDA regulated, any additional elements not included in the Common Rule requirements must also be included.

NOTE: MC IRB is not currently employing the option for broad consent as provided in 45 CFR 46. If this mechanism is employed at this institution, the policies will be updated to reflect the relevant requirements.

The investigator should note his/her general impression of the subjects understanding, including any questions that have been raised during the consent process. Where possible, the investigator should document the process in the subject's medical record and/or research record.

A subject's autonomy must be respected at all times, and the consent process must be free of all elements of coercion. The patient's ability to understand and process the information must be assessed by the person obtaining consent.

5.3 Documentation of Informed Consent

Except where a waiver is granted, obtaining initial informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. See ***Informed Consent Guidance Form*** for assistance in preparing consent forms to be used at MC.

All potential research participants should be provided with the information in the IRB approved consent form both verbally and in a copy of the consent form. They must be given ample time to think about whether or not they wish to participate, and must have the opportunity to ask questions. Ideally, the potential subject should be given the form to take home, and should be advised to think about their participation and discuss it with family and friends. If consent is obtained on the same day that research procedures are initiated, the investigator should document in the research record the date and time that consent was obtained and that it occurred prior to the initiation of the research procedures.

Consent is not valid unless the subject or the subject's legally authorized representative is fully informed about all the information in the consent document. Signatures on consent forms do not absolve the investigator of the responsibility to make sure that the subject or the subject's legally authorized representative is fully informed about the research.

Once a subject agrees to participate, the subject or the subject's legally authorized representative must sign and date the consent form in the appropriate place. The person obtaining consent must also sign the form and, in so doing, affirm that the subject has been fully informed about all aspects of the study, alternatives to participation have been discussed, and the subject willingly gives their consent to participate in the study. The person obtaining consent should sign the consent form on the date that he/she actually performed the consent process. Note: Consent for research participation must be obtained by a member of the research team credentialed to perform the intervention in the study.

One copy of the signed consent form must be given to the person signing the form (subject or representative) and a second copy should be placed in the subject's medical chart (if appropriate). The original, signed consent form must be retained in the PI's research records. Consent forms must be retained for all subjects enrolled in the study, regardless of whether they withdraw or are withdrawn. A subject is considered enrolled at the moment they sign the consent form, whether or not they actually participate in the research or any of the procedures involved. The IRB may determine that there be a witness signature on the consent form.

Consent is an ongoing process that requires the investigator to keep subjects apprised of issues that arise which may affect their willingness to continue participation. The subject's continued willingness should be documented periodically in the subject's medical record and/or research record, and in some cases a revised consent form or addendum may be appropriate. There are certain circumstances where a subject may be asked to re-consent to participation in the research study.

5.4 Waiver of Informed Consent Requirements

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent, provided one of the two following sets of criteria are met.

1. The research involves no more than minimal risk to the subjects;
2. The research could not practicably be carried out without the waiver or alteration;

3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; **AND**
5. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

OR

1. The research or demonstration project is to be conducted by or is subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in methods or levels of payment for benefits or services under those programs; **AND**
2. The research could not practicably be carried out without the waiver or alteration.

Screening, recruiting or determining eligibility

- An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subjects or the subject's legally authorized representative, if either of the following conditions are met:
    - The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
    - The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens

Posting of clinical trial consent forms

For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on the designated Federal Website that acts as a repository for such informed consent forms (e.g., clinicaltrials.gov). It may be appropriate to redact certain information from the posted consent form. The posting must occur after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

The IRB may waive the requirement to obtain authorization for the use of PHI if the following criteria are met for a waiver of HIPAA authorization to use or disclose PHI in the conduct of research:

A. The use or disclosure of PHI involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

1. An adequate plan to protect the identifiers from improper use or disclosure.
2. 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
3. Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, (except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by regulation).
4. The research could not practicably be conducted without the alteration or waiver; **AND**
5. The research could not practicably be conducted without access to and use of the PHI.

The IRB will use the criteria above in determining whether or not the consent requirement and HIPAA authorization requirement can be waived. The Principal Investigator must include a request for such a waiver in the IRB application and must provide justification for the request based on these criteria.

Note: The informed consent requirements in this policy are not intended to preempt any applicable Federal, State or local laws which require additional information to be disclosed in order for informed consent to be legally effective. Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent that the physician is permitted to do so under applicable Federal, State or local law.

FDA regulations permit a limited class of research in emergency settings without consent. See *Emergency Research* for additional instances where the requirement for informed consent may be waived.

5.5 Waiver of Documentation of Informed Consent

Consistent with 45 CFR 46.117(c), the IRB may **waive the requirement for the investigator to obtain a signed consent form** from some or all subjects if it finds that either:

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

or

- 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.

Investigators may specifically request a waiver of the documentation of the informed consent requirement by providing information that supports one of the conditions stated above. The IRB may still require submission of a consent script that will be used to verbally consent a subject, a consent letter signed by the investigator that will be used in conjunction with a survey (e.g. when survey materials are mailed), or a written statement summarizing certain elements to be provided to subjects. Both of these methods will need to comply with federal requirements regarding mandated elements of informed consent.

The IRB will use the criteria above in determining whether or not the documentation of the consent requirement can be waived. The Principal Investigator must include a request for such a waiver in the IRB application.

Note: A waiver of documentation of consent (signed consent) is not the same as a waiver of consent. A waiver of signed consent does not exempt an investigator from obtaining verbal informed consent.

[See Emergency Use Exemption from Prospective IRB Approval for additional exceptions to informed consent requirements in an emergency setting.]

5.6 Persons Authorized to Obtain Informed Consent from Research Participants

Informed consent for research involving medical/psychiatric intervention shall be obtained by a physician member of the medical staff who is familiar with all aspects of the research protocol, unless an exception is made by the IRB which allows for consent to be obtained by another investigator who is licensed to perform the intervention (e.g., RN, PsyD, etc.). Any investigator, including an investigator who is not a physician, who is familiar with all aspects of the research protocol and is listed on the protocol as a research investigator, may

obtain consent for research that does not involve medical/psychiatric intervention.

The person obtaining consent must sign the form. By so doing, he/she attests that the subject has been fully informed about all aspects of the study, alternatives to participation have been discussed, and the subject willingly gives their consent to participate in the study.

5.7 Persons authorized to give permission for a subject (other than themselves) to participate in research

Consent, or agreement to participate in a research study, shall be given by the individual who will be the research subject or a person who is permitted to act on behalf of that individual (a legally authorized representative). Persons consenting on their own behalf must be an adult over the age of 18 years whose clinical condition does not preclude them from making a sound judgment regarding the risks/benefits of participation. For adult subjects incapable of consenting to participation due to their clinical or mental condition, the IRB may approve a process whereby permission may be obtained from the subject's legally authorized representative or, **in limited cases**, next of kin. (See Research Involving Incapacitated or Decisionally Impaired Subjects).

For children, the parent or legal guardian shall be permitted to act on behalf of the child and give permission for their participation. However, the assent of the child shall be obtained from any child considered mature enough to understand (usually in the range of 7-9 years of age), unless the IRB determines that the assent requirement can be waived (see Waiver of the Assent Requirement).

All research involving children as subjects shall be placed into one of the four categories of risk as outlined at 45 CFR 46.404, 405, 406, 407. The categories are as follows:

1. Research not involving more than minimal risk. 46.404
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. 46.405
3. 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. 46.406
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (Approval of research included under this category is very rare). 46.407 Note: Research in this category needs approval of the Secretary DHHS in addition to IRB approval.

Where research is covered under Category 3 or 4 (45 CFR 46.406 or 45 CFR 46.407, and when permission is to be obtained from parents, both parents shall give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. In this case, when only one parent is giving permission, the justification for not requiring the other parent's signature shall be documented in the research record and on the consent form. When research is covered under Category 1 or 2 (45 CFR 46.404 or 45 CFR 46.405), the permission of one parent shall be considered adequate unless the IRB indicates otherwise in its approval letter.

5.8 Waiver of the Assent Requirement

The IRB may grant a waiver for the assent requirement when it is determined that there is a prospect of direct benefit, no standard approved therapy exists which is equally effective, and/or the child may not have the ability to understand the ramifications of not participating.

5.9 Re-consenting Subjects

Subjects may need to be re-consented due to changes in their status (i.e., previously enrolled by proxy and now able to consent on their own behalf) or due to changes in the protocol and/or consent form as follows:

- The protocol and/or consent form has been modified since the subject enrolled and the changes are more than administrative (i.e. the information which has been added/deleted may have an impact on risk to subjects and their willingness to participate).
- The subject was initially enrolled in a study by parents, a legally authorized representative or a research proxy because:
    - The subject was a minor at the time of entry into a study and has since reached the age of 18 and can now consent on his/her own behalf, **or**
    - The subject was incapacitated at the time of enrollment and has regained capacity to consent on his/her own behalf

In some cases it may be appropriate to provide a subject with an addendum to the original consent form which provides the new information, or to verbally inform subjects of an administrative or other minor change with documentation in the research record that such notification took place. If an addendum is used, it must clearly state that the information in the original consent form is still current and valid, and that the information in the addendum is supplementary.

5.10 Expiration of Consent

The process of informed consent shall take place no more than 30 days prior to the initiation of the research. If more than 30 days has elapsed since the subject provided consent, the process shall be repeated. The same requirements for signatures and obtaining consent apply when re-consenting or presenting an addendum to a study subject.

5.11 Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English

Department of Health and Human Services regulations for the protection of human subjects require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (45 CFR §46.116 and §46.117).

Where informed consent is documented in accordance with §46.117(b)(1), the written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a consent document written in a language understandable to them.

Alternatively, §46.117(b)(2) permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary.

When this procedure is used with subjects who do not speak English,

1. The oral presentation and the short form written document should be in a language understandable to the subject;
2. The IRB-approved English language informed consent document may serve as the summary; and
3. The witness should be fluent in both English and the language of the subject.

At the time of consent,

1. The short form document should be signed by the subject (or the subject's legally authorized representative);
2. The summary (i.e., the English language informed consent document) should be signed by the person obtaining consent as authorized under the protocol; and

3. The short form document and the summary should be signed by the witness. When a translator assists the person obtaining consent, the translator may serve as the witness. **Contact IRB Chair or the short form template.**

Informed Consent Translations
Investigators conducting research in which it is **anticipated** that a non-English speaking population will be included should submit a foreign-language consent, as appropriate, at the time of initial submission.

5.12 Obtaining and Documenting Informed Consent of Illiterate Subjects

A person who can comprehend English but cannot speak or write can be enrolled into a research study if they are otherwise competent and able to communicate approval or disapproval. The subject may be asked to "make his/her mark" on the consent form. The person shall be provided with a verbal explanation of the study, and the consent form shall be read to them and explained in detail. All of the other requirements of informed consent must be followed. The consent form should document the way in which information was conveyed to the subject, and the means by which the subject communicated agreement to participate in the study. An impartial third party must witness the entire consent process and sign the consent document.

5.13 Mailed/Emailed/Faxed Consent/Authorization Forms

With IRB approval, research subjects may participate in studies in which they do not have to meet directly with the investigator (i.e., questionnaires, buccal smears, prospective chart reviews, etc.). In general, informed consent and authorization may be initiated and obtained through the following methods as recruitment policy allows (see Policy 4). The IRB may request additional steps/procedures depending on the study.

1. Telephone Contact

a. Investigator may contact (or be contacted by) a potential subject by telephone to discuss participation in a research study. Investigator must provide subject with all the information contained in the written consent form.

b. Investigator will answer any questions regarding the research and give subject ample time to consider participation in the study. (May require follow-up phone conversation).

c. If subject indicates interest in participating in the research study, investigator will provide his/her contact information. Investigator will explain (and repeat) the next steps necessary for subject to provide informed consent, which include the following:

i. A written consent form will be sent to the subject by regular mail or as an email attachment;

ii. The subject must read the consent form and call or email the investigator if he/she to discuss research and resolve issues/questions;

d. If subject agrees to participate in research, investigator should direct him/her to initial all pages, sign the consent form and return it to the investigator by mail or fax. Another option would be to scan the signed consent form to a PDF file and return it to the investigator as an email attachment.

e. An enrollment note must be written by the investigator documenting all phone conversations with the subject. Printouts of any email correspondence must be placed in the subject's file.

f. After the signed consent form is received, investigator will sign the consent form. A copy will be made and sent to the subject for his/her records.

2. Email

a. Investigator may contact (or respond to) a potential subject by email – providing him/her with an attachment of the written consent form to download. In his email message, the investigator should:

i. give a brief description of the research;

ii. invite subject to download and read the consent form

iii. ask subject to contact him/her by telephone or email to discuss research and resolve issues/questions

b. If subject agrees to participate in the research, investigator should direct him/her to initial all pages, sign the consent form and return it to the investigator by mail or fax. Another option would be to scan the signed consent form to a PDF file and return it to the investigator as an email attachment.

c. An enrollment note must be written by the investigator documenting any phone conversations with the subject. Printouts of all email correspondence must be placed in the subject's file.

d. After the signed consent form is received, investigator will sign the consent form. A copy will be made and sent to the subject for his/her records

3. Letter

a. Investigator may send a letter to the subject by regular mail and include a copy of the written consent form. In his/her letter, the investigator should:

i. give a brief description of the research;

ii. invite subject to read the consent form

iii. ask subject to contact him/her by telephone or email to discuss research and resolve issues/questions

b. If subject agrees to participate in the research, investigator should direct him/her to initial all pages, sign the consent form and mail or fax it to the investigator. Another option would be to scan the signed consent form to a PDF file and return it to the investigator as an email attachment.

c. An enrollment note must be written by the investigator documenting all phone conversations with the subject. Printouts of any email correspondence must be placed in the subject's file.

d. After the signed consent form is received, investigator will sign the consent form. A copy will be made and sent to the subject for his/her records

4. Fax

a. Investigator may fax a letter to the subject with a copy of the written consent form. In his/her fax, the investigator should:

i. give a brief description of the research;

ii. invite the subject to read the consent form

iii. ask the subject to contact him/her by telephone to discuss research and resolve issues/questions

b. If the subject agrees to participate in the research, investigator should direct him/her to initial all pages, sign the consent form and send it to the investigator by mail or fax. Another option would be to scan the signed consent form to a PDF file and return it to the investigator as an email attachment.

c. An enrollment note must be written by the investigator documenting all phone conversations with the subject. Printouts of any email correspondence must be placed in the subject's file.

Note: Although fax and PDF copies are acceptable forms of documentation, investigators should strongly encourage participants to mail them the original signed consent forms.

If a consent form is returned **missing a signature or without all the pages initialed**, the participant will be notified by phone or email. A copy will be made and kept in the participant's file and the original will be sent back to the participant for completion and resubmission to the investigator.

Policy 6: Continuing Review of Ongoing IRB-Approved Research

IRB Approval periods are granted on the basis of degree of risk associated with a particular protocol. An approval period will not exceed one year. As detailed in Policy 1, certain projects may require review more often than annually based on other factors other than degree of risk (e.g. past history of non-compliance with a particular investigator, requiring more stringent oversight by the committee).

Once approved, the IRB shall conduct continuing review of all research activity in compliance with 45 CFR 46 and 21 CFR 56. Continuing review is required for all research protocols approved by the IRB (unless the protocol was determined to be exempt by the IRB at submission) for the duration of the research, at least as long as individually identifiable follow-up data are being collected or analyzed, and regardless of whether a protocol has been closed to enrollment or whether the interventional portion of the research is complete.

Continuing review includes, but is not limited to, progress reports, re-activation of terminated protocols, audits, modifications, protocol exceptions, protocol violations, serious adverse events/unanticipated problems, termination/withdrawal of protocols, and any other activity that the IRB determines necessary for monitoring ongoing research. The IRB also has the authority to inspect records and to observe (or have a third party observe) the consent process and the research activity for any protocol that it approves.

Note: Unless the IRB determines otherwise, continuing review of research is not required in the following circumstances:

- Research eligible for expedited review in accordance with 46.110
- Research reviewed by the IRB in accordance with the limited IRB review described in 46.104(d)(2)(iii) or (d)(3)(i)(C).
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB approved study:
  - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

It is the responsibility of the principal investigator (PI) to comply with continuing review requirements.

6.1 Progress Reports

According to federal regulations, a research protocol can only be approved for a maximum of 365 days. Within that time period, continuing review is conducted at intervals specified at the time of initial approval. Those intervals are based on the degree of risk to study subjects. If the risk/benefit ratio changes at any time during the study, the IRB has the authority to modify the continuing review interval and/or request changes to the protocol. The IRB also has the authority to require additional information at any time or to request an audit of the research to assure the safety of subjects and compliance by the research team.

To renew the approval period, the PI must submit a progress report and any requested relevant documents to the IRB before the project's expiration (the date at which the current approval ends). Since the IRB does not have the authority to extend the approval period beyond the expiration date, it is essential that the PI submit a complete progress report by the due date set by the IRB.

While the IRB will in most cases forward a request for the renewal information in advance of the project's expiration date, the responsibility rests with the PI to submit timely renewal requests. **If the PI successfully complies with the progress report request by the due date set by the IRB, the study will be presented at the next convened IRB meeting for renewal**.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically.

If a progress report is submitted and received prior to the expiration date but is deficient, the Office of the IRB will contact the PI with details regarding the deficiencies. If a complete and correct progress report is not received within the required time frame, the project is subject to the same warning/suspension and termination procedures outlined above. The IRB is not authorized to extend the approval period for any research project.

Note: Federal guidance indicates that short-term continuation of the research procedures beyond the IRB approval date may be permissible for the safety of research subjects who are enrolled in research projects that involve therapeutic intervention or interaction, if the investigator is actively pursuing renewal with the IRB, and the IRB believes that over-riding safety concerns or ethical issues is involved. There must be notification to the Office of the IRB of all such situations, including a justification for interaction while the study is in the process of being re-activated. It is critically important that the investigator re-activate the protocol rapidly (see Re-activation of Terminated Protocol).

6.2 Re-activation of Terminated Protocols

A protocol that has been terminated, ***for any reason***, cannot be re-activated unless it is re-reviewed and approved by the IRB. If a PI wants to re-activate a terminated protocol, he/she must submit a progress report within 90 days of the expiration date. If a progress report is not submitted within 90 days of the expiration date, the PI must resubmit it to the IRB as a complete application packet in accordance with the requirement for new protocols. (See Policy 2: Materials Required for IRB Submission).

In addition to the protocol application, the PI must submit a memorandum to the IRB, detailing the circumstances that led to the protocol closure, along with his/her reasons for re-activating the protocol. If termination was due to administrative problems (e.g., a delinquent progress report), he must include a description of the corrective action he/she has taken in order to avoid such closures in the future.

6.3 For-Cause Compliance Audits

When necessary, the IRB may request information beyond regular progress reports in order to ensure that the rights and welfare of research subjects are protected. Upon discovery of a potential problem, the IRB or IRB chair/designee will consider the issues and has the authority to suspend a protocol if a deficiency or situation poses a risk to subjects.

The IRB will notify the PI in writing that an audit has been requested. The letter will outline the reason for the request and detail any information that is needed. The PI will be given adequate opportunity to respond. The IRB staff or designee will arrange a time to review the investigator's study files and any other information necessary for the conduct of the audit. The IRB shall be kept apprised of any such action at their monthly meeting. If the audit indicates monitoring is necessary to investigate an immediate concern regarding the safety of study subjects, the IRB chair/designee may act accordingly without convening an IRB meeting, however, no protocol may be permanently terminated without the concurrence of the committee at a convened meeting.

Under HHS regulations, a for-cause suspension of IRB approval must be reported to OHRP. Any suspension resulting from a for-cause audit will be immediately reported to the Institutional Official, department chair, funding agency (if applicable), OHRP, and, if a drug or device is involved, the FDA.

For-cause audits may also be prompted by information obtained from sources outside the IRB, such as internal/external whistleblowers, regulatory agencies, industry sponsors, or research subjects.

6.4 Routine Audits

There may also be routine audits of IRB approved studies. The IRB will select the studies to be audited.

The goals of the routine audits are to:

- Assure protection of human subjects and data integrity
- provide education and training to research staff,
- ensure that federal, state and institutional regulatory standards are

The IRB Office will notify the PI in writing about the audit and will arrange a time to review the investigator's study files.

The audit process will usually

- inspection of the IRB files for the study,
- on-site review of the investigator's files and records,
- review of the informed consent process, form and any other documents deemed appropriate.

The auditor will generate a report that will include a summary of the audit findings and recommendations. The PI will be sent a draft version of the study audit report for review and will have adequate opportunity to respond with comments. A final version will be submitted to the PI for signature and a copy will be provided to the IRB. A summary report of routine audits will be presented to the IRB on an ad hoc basis with any recommendations for remedial action. The IRB will follow up with investigators requiring action when needed.

Note: Significant findings may also be reported to external authorities as required (OHRP, FDA, etc.).

6.5 Modifications

Changes (amendments/modifications) to a protocol **may not** be initiated without prior IRB approval, except when necessary to eliminate **immediate** hazards to the subjects. When changes are implemented to eliminate an immediate hazard, the IRB must be notified of the change promptly (within 3-5 business days).

Major modifications are changes to the protocol that alter the risk/benefit ratio for study subjects, that significantly change or affect the conduct of the study, and include any new information that may affect safety and/or willingness of subjects to participate.

Minor modifications are changes that do not alter the overall risk-benefit profile of the study, would not potentially affect the willingness of enrolled subjects to

remain in the study, or the willingness of potential subjects to enroll in the study, and do not alter the scientific validity of the study design.

It is the responsibility of the PI to submit, in a timely manner, all protocol modifications, revised consent forms, changes in investigators, changes to FDA Form 1572 (for clinical trials), and any other information which may affect the conduct of the research study.

Minor changes in the protocol and/or consent form, may be reviewed through the expedited review procedure. However, all other changes will be reviewed by the IRB at a convened meeting.

IRB approval of amendments does not change the expiration date for the protocol. The current approval period for the protocol remains the reference point for continuing review requirements.

6.6 Protocol Exceptions

A protocol exception is any **temporary** protocol deviation that is approved by the IRB ***prior to its initiation***, e.g., enrollment of a subject who does not meet the eligibility criteria. An exception request gives investigators the opportunity to request a change in procedure and/or protocol activity for a single, isolated event.

The PI should only request approval for exceptions that could affect a subject's safety, welfare, comfort or rights. For example, a minor scheduling change does not need to be approved prior to implementation.

In order to obtain approval for a protocol exception, the PI must submit a request to the IRB. The request should include:

- A description of the requested exception
- Justification for deviating from the protocol

All approved protocol exceptions should be listed on the progress

The Office of the IRB will process protocol exception requests. Each request will be evaluated on a case-by-case basis by the IRB chair or designee, and when appropriate, by the convened IRB committee.

Investigators will be informed in writing regarding the IRB's decision. No exception may be implemented without IRB approval.

6.7 Protocol Violations

A protocol violation is a **deviation that is not approved by the IRB** prior to its initiation or implementation. Protocol violations may be major or minor:

A **major protocol violation**:

- Affects subject safety
- Damages the scientific integrity of the data collected
- Affects a subject's willingness to participate in the

A **minor protocol violation**:

- Does not affect subject safety
- Has no effect on value of the data collected
- Does not affect a subject's willingness to be in a

Examples of **major protocol violations** include (but are not limited to):

- Failure to obtain informed consent (i.e., no documentation of informed consent, consent obtained after study procedures were initiated)
- Informed consent for IND/IDE studies obtained by unauthorized individuals (i.e., someone other than a licensed physician investigator)
- Enrolling subject who does not meet inclusion/exclusion criteria
- Use of study procedures not approved by the IRB
- Failure to report serious adverse event to the IRB and/or sponsor
- Failure to perform a required lab test that could affect subject safety or integrity of data
- Error in dispensing or dosing of drug/study medication
- Error involving use of device
- Study visit conducted outside of required timeframe, **only if it affects subject safety**
- Failures to follow safety monitoring plan
- Failure to submit continuing review application to the IRB before study expiration
- Missing subject signature on consent form
- Use of invalid consent form (outdated or unapproved version).
- Enrollment of subjects after IRB approval of study has expired.

Examples of **minor protocol violations** include (but are not limited to):

- Missing original signed and dated consent form (only photocopy available)
- Inappropriate documentation of informed consent, including:
    - Copy not given to the person signing the form
    - Someone other than the subject dated the consent form

- Deviations from the approved study procedure that do not affect subject safety or data integrity
    - Study procedure conducted out of sequence
    - Omitting an approved portion of the protocol
    - Failure to perform a required lab test
    - Missing lab results
    - Study visit conducted outside of required timeframe
- Failure of subject to return study medication

It is the responsibility of the PI to determine if a violation is major or minor. **Major protocol violations must be reported to the IRB within ten (10) working days of discovery**. Minor protocol violations may be reported at continuing review. Reports of protocol violations should be submitted to the sponsor according to the sponsor's protocol.

If the protocol violation is major, it should be immediately submitted to the Office of the IRB.

If the protocol violation is minor, it may be reported and detailed on the Progress Report form at the time of continuing review.

Reports of protocol violations are reviewed by the IRB chair. The IRB chair may initiate further inquiry or review, depending on the violation. If the violation proves to be serious, the IRB chair may choose to suspend or terminate the protocol.

When a protocol has been suspended or terminated due to a major violation, the action will be reported to the Vice President for Academic Affairs (Institutional Official), the department head, the FDA (as appropriate), any funding agency and the OHRP. Any subsequent action, such as changing or lifting a suspension will also be reported to the appropriate agencies or department heads. Investigators will be informed in writing of all IRB inquiries and determinations.

6.8 Adverse Events / Unanticipated Problems

Investigators are responsible for prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others. The IRB, in its initial determinations, assesses the risk/benefit ratio inherent in a given proposed research activity involving human subjects. Once the study is initiated and ongoing, the IRB depends on the investigator to promptly inform them of any unanticipated problems involving risks to subjects or others, including serious adverse events, that occur in subjects enrolled in their studies.

The IRB will assess the relationship of these problems/events to the subjects' participation in the study, as these negative effects may obviously affect the

risk/benefit ratio. As a result of the assessment, the IRB may determine that the study protocol and/or consent forms need to be updated, and/or currently enrolled subjects need to be informed of the new information to determine whether or not they wish to continue. In some cases, the IRB may determine that the risk to subjects has changed enough that the study must be stopped (perhaps even temporarily until a thorough assessment can be made).

Definitions

Adverse event: An adverse event (AE), as defined by Good Clinical Practice, is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease having been absent at baseline, or, if present at baseline, appears to worsen AND is temporally associated with treatment or procedure, REGARDLESS of the attribution (i.e., relationship of event to medical treatment or procedure).

An **adverse event** can include:

- an abnormal laboratory finding,
- unfavorable symptom, disease, or occurrence, or
- any other unanticipated event involving risk to subjects or others in a research study, whether or not considered related to the product, device, treatment, research procedure, or behavioral intervention being studied.

Serious Adverse Event (SAE): Any adverse event that -

- results in death,
- is life-threatening (i.e. the subject was at risk of death at the time of the event. It does not include events that hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- results in unanticipated serious risk/harm to subjects and others.

Unexpected adverse event: Any adverse event not identified by nature, severity and frequency in the protocol or the investigator's brochure.
Unanticipated problem: Any harmful or unfavorable non-medical occurrence or any development that -

- potentially increases the likelihood of harm occurring to a subject or others in the future, or
- affects the validity of the research

Note: Unanticipated problems can be "acts of God", power failures, breaches of

confidentiality, loss of study data, etc. since they could have an adverse effect on study subjects.

Internal Adverse Events

An internal adverse event is one that occurs to a subject enrolled in a study at a research site under the jurisdiction of the MC IRB.

Note: If MC is functioning as the coordinating center for a multi-site study, the PI must treat any adverse events from the involved sites as internal adverse events and report them according to MC policy.

Reporting Requirements for Internal Adverse Events

All **internal, serious adverse events that are expected and unexpected** which occur during a study, or in a post-study period of reasonable duration (i.e. during follow-up), **MUST be reported** to the IRB and the study sponsor, as appropriate, **within 2 business days** of occurrence or knowledge of event by the

Any internal events that are expected but not serious should NOT be submitted.

Reports should identify subjects by unique code numbers rather than by subjects' names, personal identification numbers, and/or addresses.

The IRB may determine that modifications be made to the consent form and/or protocol to assure the safety and willingness of the subjects to remain in the study.

External Events

An external adverse event is one that involves a subject enrolled at a facility that is outside the jurisdiction of the MC IRB (e.g., safety report from sponsor, collaborating site, Data Safety Monitoring Board (DSMB) report, etc.).

Reporting Requirements for External Adverse Events

The FDA requires sponsors to notify all participating investigators of any serious and unexpected adverse event associated with the use of a test article that occurs at one of the participating sites of a multi-center study. These reports must be submitted to the IRB by the investigator as they are received if the events are deemed related to the study agent. An assessment must be made by the principal investigator to determine whether or not a change to the consent form is necessary as a result of the information in the report. If reports are received by an investigator in the form of a series of safety reports, or a periodic Data Safety Monitoring Board (DSMB) Report (often a compilation of adverse

events), and meets the reporting requirements outlined above (i.e., serious, unexpected and related events) the investigator shall provide a written summary to the IRB along with the report.

When sponsor submission requirements and IRB policy are discordant, the IRB policy shall be followed.

The following types of external serious adverse event reports should NOT be sent to the Office of the IRB:

1. Expected events
2. Unrelated events

If the Office of the IRB receives any reports that fit these two criteria, they will be filed without acknowledgement.

How to Report an Adverse Event to the IRB

PI to contact IRB within timeframe guidelines in this document (via irb@molloy.edu with PI name, protocol name and IRB #, and description of the event. The IRB Chair or Administrator will provide form for completion after email received from PI.

All reportable events should be submitted to the IRB as

- For serious internal adverse events, in addition to the appropriate form, the investigator's report should include:
    - A detailed description of the event
    - Category of event - expected or unexpected
    - Any resultant changes to the consent form
    - Event relation to study intervention
    - Rationale for assessment
    - Outcome
    - Site of incident

Note: For internal reportable events, the PI must attach supporting information and materials such as progress notes, lab findings, death certificates, etc.

For serious external adverse events. The investigator's report should

- A detailed description of the event
- Any resultant changes to the consent form
- MC investigator's assessment of event

- Site of incident

Note: For external reportable events, the PI must attach supporting information and materials such as letters from sponsor, MedWatch reports, site investigator reports, progress notes, etc.

For unanticipated problems involving risks to subjects or others. The investigator's report should include:

- A detailed description of the event
- Effect on subjects
- Effect of study validity
- Corrective action

Note: The PI is the sponsor of investigator-initiated studies. As such, he/she must follow mandatory FDA reporting requirements. (See www.fda.gov/medwatch/how.htm). Copies of any reports submitted to the FDA should be sent to the IRB.

IRB Response/Action

The IRB will review all reported internal serious adverse events and will evaluate the protocol and the consent form to determine if changes are needed.

All such events will be acknowledged by the IRB according to their severity and relation to the study.

External serious adverse events that are unexpected and possibly, probably, or definitely related will be stamped and filed. The IRB committee will not review them. A copy of the stamped IRB Form will be sent to the PI. Follow-up reports will be stamped and filed, unless there is a significant change in the assessment of causality. If a study is closed to patient entry and no subjects are on active treatment, the reports will be stamped and filed, unless a change to the protocol alters the follow-up procedures for patients.

The IRB or IRB chair/designee has the authority to suspend, and the IRB has the authority to terminate, approval of research at its site that has been associated with unexpected serious harm to participants. When the IRB or IRB chair/designee takes such action, a statement of reasons for such action shall be included in a notification letter to the PI. The IRB or IRB chair/designee shall promptly report its findings to the investigator and, if warranted, to Institutional officials, study sponsor, Office of Human Research Protection (OHRP), and the FDA.

6.9 Termination of a Protocol

The following are two different mechanisms by which a protocol may be terminated:

1. **Voluntary termination** by the investigator or sponsor (study ends, investigator leaves the institution, etc.).
2. **Administrative termination** by the IRB due to safety concerns, investigator non-compliance, delinquent progress reports (failure to renew a protocol prior to expiration of IRB approval), failure to submit annual report for studies that do not undergo a formal continuing review.

If a study is voluntarily terminated, it is requested that the PI notify the IRB by completing and submitting a Study Progress/Termination Report.

If a protocol is **administratively terminated**, the IRB Chair/designee will notify the PI in writing that the protocol has been terminated by the IRB or IRB Chair due to delinquent progress reports, concern for safety of human subjects, non-compliance, etc. In a case of immediate hazard to subjects, initial notification may be in the form of a telephone call or e-mail from the IRB Chair or designee.

6.10 Withdrawal of a Protocol

If a PI decides not to implement an IRB approved study, a written request for study withdrawal must be sent to the IRB.

6.11 Other Activity as Determined by the IRB

The IRB has the authority to request additional information, as necessary, to assure patient safety and compliance with federal and state regulations and institutional policy.

Policy 7: Additional Protections for Certain Populations

Research involving certain populations requiring additional protection as per 45 CFR 46 will be reviewed and conducted according to regulations of the Department of Health and Human Services (DHHS) – Subparts B (fetuses, pregnant women, and in vitro fertilization), C (prisoners), and D (children) of the DHHS regulations (45 CFR 46) and FDA regulations (21 CFR 50) subpart D, as well as New York State law governing such research.

Vulnerable populations include those whose diminished autonomy compromises their ability to give informed consent to participate in research. Additional protections are also warranted for pregnant women who, although not vulnerable, are afforded additional protection under Subpart B. Children, pregnant women, fetuses, individuals with impaired decision making capacity, prisoners, and the economically or educationally disadvantaged are among the groups most often identified as being vulnerable or needing additional protection. However, depending on context or circumstances, students, employees, patients in emergency rooms, institutionalized persons and people who are not fluent in English may also be considered vulnerable. As a rule, anyone in a situation where his or her ability to give informed consent is compromised or eliminated should be considered vulnerable or a population for which additional protections are warranted.

7.1 Research Involving Children (<18 years of age)

Reference: 45 CFR 46 Subpart D

Children are considered a vulnerable research population because their emotional and intellectual capacities may be limited and they are not of a legal age to give informed consent. The IRB is responsible for assuring that Principal Investigators conducting research with children comply with additional requirements as set forth by the DHHS in 45 CFR 46 Subpart D and FDA regulations at 21 CFR 50 Subpart D. During its deliberations, the IRB will consider the degree of risk and potential benefit of the proposed activity and whether it is appropriate to obtain the assent of the minor.

Definitions:

Assent: A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Children: Persons who have not attained the legal age to give consent for their own medical or dental care. A person is deemed to be a minor in New York

State if he is under 18 years old (age of majority is reached the day prior to the individual's birth date).

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by NYS law (18 years of age), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage, or procreation.

Guardian: An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical or dental care

Minimal Risk: 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 routine physical or psychological examinations or tests.

Parent: A child's biological or adoptive

Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research.

Additional Protections of Minors:

Additional protections that must be considered in all research activities in which minor are, or may be, included are:

1. **Obtaining parental permission** (in most cases). The exception being if the IRB determines that a research protocol is designed for conditions, or for a subject population, for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children). In such cases, an appropriate mechanism for protecting the children who will participate as subjects in the research must be in place, and the waiver must be consistent with other applicable federal, state, and local regulations.
2. **Obtaining minor assent**, except where the IRB specifically grants a waiver. In determining whether children are capable of assenting, 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 research under a particular protocol, or for each child. The IRB may require documentation of assent, such that the minor is presented with an assent form to review and sign.

The IRB may determine that the assent of the minor is not a necessary condition for proceeding with the research if:

- The capability of some or all of the children is so limited that they cannot reasonable be consulted
- That the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research
- The IRB determines that assent can be waived under circumstances in which consent can be waived.

3. Allowance of participation in only certain categories of

The IRB will determine the risk/benefit ratio for the protocol using one of the following four categories

a. Research not involving greater than minimal risk.
b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject.
c. Research involving greater than minimal risk and no prospect of direct benefit to the subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, as long as the following conditions are met:
    i. The risk represents a minor increase over minimal risk
    ii. The intervention or procedure presents experiences to the subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations.
    iii. The intervention or procedures 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 condition; and
    iv. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.
d. Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children, if the following conditions are met:
    i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, in which case the assent of the children and the permission of their parents or guardians are to be obtained; and
    ii. The Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (e.g. science, medicine, education, ethics, law) and following the opportunity for public review and comment, that the research in fact satisfies the above criteria, or (1) the research presents a reasonable opportunity to further the understanding,

prevention, or alleviation of a serious problem affecting the health and welfare of children; (2) the research will be conducted in accordance with sound ethical principles,; and (3) adequate provisions are made for soliciting the assent of the children and the permission of their parents/guardians.

Permission by Parents or Guardians

When children are involved in research, federal regulations require the permission (consent) of the parent(s) or legal guardian(s), in place of the consent of the minor subject. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under Categories a and b (45 CFR 46.404 or 46.405).

Where research is covered by Categories c and d (46.406 and 46.407) and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

If the research is designed for conditions or for a subject population for which parental/guardian permission is not a reasonable requirement to protect the subjects (i.e. neglected or abused children), the IRB may waive the consent requirement but must provide an appropriate mechanism for protecting the children.

Assent by Children

Although they are legally incapable of giving informed consent, children (generally 7-9 years of age or older) may possess the ability to assent, or refuse participation in a research study. Assent is a child's affirmative agreement to participate in a research study. Failure to object to participation cannot be construed as assent [45 CFR 46.402(b)] and assent is not valid if coerced.

Assent is always required when the research:

1. Does not involve interventions with the prospect of benefit to the subject, and
2. The child is able to comprehend and appreciate what it means to be a volunteer for the benefit of others.

A plan for obtaining assent (or justification for a waiver of assent) must be included as part of the protocol for any study involving children.

A child who is asked to assent should be given an explanation of the proposed research procedures in a vocabulary and language that is appropriate to the child’s age, experience, maturity, and medical condition. This explanation should

include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to be in the study.

Assent must be respected. If assent is solicited, the investigator must abide by the child's decision. If the child refuses to assent to participation in a study, and the IRB has determined that assent of the child is required, the child's parent(s) or legal guardian may not override the child's decision.

To obtain valid written assent, the investigator must use an IRB approved assent form. Upon reaching age 18, the subject should sign the IRB approved adult consent form for the study.

Note: While federal regulations do not require that the subject, upon maturity, sign the adult consent form, the IRB recommends that this be done to respect the subject's autonomy.

The IRB will determine that adequate provisions are made for soliciting the assent of children, when, in their judgment, the children are capable of providing assent. In order to make that judgment, the IRB will consider the ages, maturity and psychological state of the subjects. This judgment may be made for all children to be involved in research under a particular protocol, or on an "as appropriate" basis for each child, as the IRB deems appropriate.

Documentation of Permission and Assent

In cases where permission of a parent/guardian is required, it must be documented in accordance with informed consent requirements (see Informed Consent). For research where assent is also required, the IRB will determine whether and how it is to be documented. Generally, the use of an assent form is appropriate.

Waiver of Assent

If an investigator believes that assent is not appropriate, a waiver must be specifically requested, described, and justified in the protocol.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under the same circumstances in which consent may be waived. (See Policy 5.2: Waiver of Informed Consent Requirements).

Emancipated Minors

Individuals under the age of 18 who are considered emancipated minors by New York State may be able to consent to research participation for themselves. Although not specifically addressed by NYS statute, there may be instances where participation in a clinical trial is the subject's only way to receive a particular form of treatment that may be beneficial. The IRB shall consider the inclusion of emancipated minors in research, absent parental or guardian consent, on a case-by-case basis. The IRB shall consider the subject's ability to comprehend what is being proposed, and the intervention or procedure involved in the research must offer a prospect of direct benefit that is important to the health or well-being of the minor and is not available outside the context of the research protocol.

Children Who are Wards

NOTE: The enrollment of wards of the state in any research protocol must be prospectively approved by the IRB before the subject is enrolled.

Children who are wards of the State or other agency, institution or entity, can be included in research under categories 1 and 2 without any additional requirements posed by their status.

However, they may only be included in research under categories 3 and 4 if such research is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institution, etc., in which the majority of the children involved are not wards.

Research approved under categories 3 and 4 shall require the 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. The IRB will be responsible for appointing 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 part in the research. The advocate must not be associated in any way (except in the role as advocate) with the research or clinical investigation, the investigator(s), or the guardian organization. When circumstances allow, a member of the IRB may serve as an advocate. One individual may act as advocate for more than one child.

The advocate must be present during the Informed Consent process and be available throughout the duration of the research to address any questions or concerns encountered by the subject. The PI will send reports on the subject's participation to the advocate at regular intervals. The IRB will determine the

frequency of that reporting based on issues including the level of risk to subjects on a protocol by protocol basis.

IRB Review of Research Involving Children

Protocols involving children will be assigned to reviewers with the appropriate expertise to evaluate the use of the procedure/intervention in a pediatric population. The IRB will determine which category of risk is applicable to an individual protocol and conduct its review accordingly.

Types of Activities involving minors that may qualify for exemption or expedited review

1. The exemption review category, and corresponding review procedure, as outlined in Policy 1, applies to research involving minor subjects with the exception of exemption #2. The exemption for research involving survey or interview procedures or observation of public behavior does not apply to research with minors, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
2. The expedited review category and corresponding review procedure, as outlined in Policy 1, is applicable to research involving minor subjects, as long as the particular activity in that section does not require that the subject be 18 years of age or older.
3. All other research involving minor subjects must be reviewed by the full committee.

7.2 Research Involving Pregnant Women, Human Fetuses, and Neonates

Reference: 45 CFR 46 Subpart B

All research involving pregnant women, human fetuses and neonates shall be conducted and reviewed in compliance with the additional DHHS requirements as set forth in 45 CFR 46 Subpart B.

Definitions

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

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

Fetus: the product of conception from implantation until

Neonate: a newborn

Nonviable neonate: a neonate after delivery that, although living, is not

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

Viable: being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Research Involving Pregnant Women or Fetuses

Pregnant women or fetuses may be involved in research if **all** of the following conditions are met:
(A) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(B) If the research offers the prospect of **direct benefit for the pregnant woman or the fetus** where:

1. The risk to the fetus is caused solely by the research interventions or procedures **and**
2. The risk to the fetus is **NOT** more than minimal risk and
3. The risk is the least possible to achieve the objectives of the research **and**
4. Informed consent is obtained from the pregnant woman in accord with the provisions of subpart A

(C) If the research offers the prospect of **direct benefit solely for the fetus** where:

- The risk to the fetus is caused solely by the research interventions or procedures **and**
- The risk to the fetus is NOT more than minimal risk **and**
- The risk is the least possible to achieve the objectives of the research **and**
- Informed consent is obtained from the pregnant woman **and the father** in accord with the provisions of subpart A

Note: The father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, temporary incapacity or the pregnancy resulted from rape or incest.

(D) If the research offers no prospect of direct benefit for the pregnant woman or the fetus where:
· The research is the development of important biomedical knowledge which cannot be obtained by any other means; and

- The risk to the fetus is caused solely by the research interventions or procedures **and**
- The risk to the fetus is NOT more than minimal risk **and**
- The risk is the least possible to achieve the objectives of the research **and**
- Informed consent is obtained from the pregnant woman in accord with the provisions of subpart A

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

Note: In New York State, any person who is pregnant, regardless of age, may give effective consent for medical, dental, health and hospital services relating to prenatal care. (Source: NYS Public Health Law, Section 2504)

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

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

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

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

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

(2) Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

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

(4) The requirements of the following sections, “Neonates of Uncertain Viability” and “Nonviable Neonates”, have been met as applicable.

Neonates of Uncertain Viability
Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following **additional** conditions have been met:
(1) The IRB determines that:

- The research offers the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with 45 CFR 46 subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

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

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;

3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent will suffice.

Note: The consent of the father need not be obtained for research involving a nonviable neonate if the pregnancy resulted from rape or incest.

The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will **not** suffice.

Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of 45 CFR 46 subparts A.

Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

1. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
2. If information associated with material described in paragraph (a) above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of 45 CFR 46 are applicable.

Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses, or Neonates

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

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

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity

for public review and comment, including a public meeting announced in the Federal Register, has determined either:

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

(2) The following:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
- The research will be conducted in accord with sound ethical principles; and
- Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

PROCEDURES

All Principal Investigators proposing such research activities will include, as part of their presentation to the IRB, assurances as to the following:

- Appropriate studies on animals and non-pregnant individuals have been completed;
- Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity;
- Individuals engaged in the activity will have no part in: (i) any decisions as to the timing, method and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy;
- No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity;
- No inducements, monetary or otherwise, may be offered to terminate pregnancy for the purposes of the activity

7.3 Research Involving Prisoners

Reference: 45 CFR 46 Subpart C

All research involving prisoners shall be conducted and reviewed in compliance with the special DHHS requirements as set forth in 45 CFR 46 Subpart C.

The IRB is responsible for assuring that Principal Investigators conducting research with prisoners comply with special requirements as set forth in 45 CFR Subpart C. Prisoners may be under certain constraints because of their incarceration, which could affect their ability to make a truly voluntary and un-coerced decision whether or not to participate as subjects in research. Therefore, additional safeguards exist in order to further protect prisoners involved in research activities.

Definitions

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

Minimal Risk: The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Permitted Research Involving Prisoners

Biomedical or behavioral research involving prisoners as subjects may only be conducted if the IRB has approved the research under the regulations as outlined above, and the Secretary, DHHS, determines that the proposed research involves solely the following:

- A study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and nor more than inconvenience to the subjects;
- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the research presents no more than minimal risk and no more than inconvenience to the subjects;
- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults). The study **may proceed only after the Secretary DHHS has**

consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register**, of his intent to approve such research;** or

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

PROCEDURES

Protocol Requirements for Research Involving Prisoners

Protocols involving prisoners submitted for approval to the IRB must include the following:

- Justification for the use of prisoners in the study
- Study objectives or study aims
- Study procedures
- Customary treatment or services at the prison (or alternative to incarceration) research site(s) for the condition being studied
- Description of how risks specific to a prison (or alternative to incarceration) setting are minimized
- Whether a Certificate of Confidentiality was obtained by the Principal Investigator (PI) for the study
- Description of recruitment procedures in the specific prison (or alternative to incarceration) setting
- Description of how the consent form was modified for use with a prison population or specific prisoner and whether a subject who is incarcerated subsequent to enrollment in a study will be re-consented

In addition, the Principal Investigator must submit all other required documents for protocol submission to the Office of the IRB. (See Policy 2: How to Submit a Protocol to the IRB).

IRB Review of Research Involving Prisoners

In addition to satisfying the requirements of 45 CFR 46.116 and 46.117, the IRB will comply with the following requirements when reviewing protocols involving prisoners as subjects:

- A majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB. 45 CFR 46.304(a)

- At least one member of the IRB will be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. 45 CFR 46.304(b)

The IRB shall consider the following when reviewing research involving prisoners:

- The research must fall under one of the permissible categories outlined above (See Permitted Research Involving Prisoners).
- Any possible advantages accruing to the prisoner through his/her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his/her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language that is understandable to the subject population;
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his/her parole; **and**
- Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Subjects Who Become Prisoners After Enrollment in Research

When a subject becomes a prisoner or is detained in an alternative facility in lieu of prison **after** enrollment in a research, the PI must notify the IRB immediately.

If the relevant research protocol was **NOT** reviewed and approved by the IRB in accordance with the requirement of HHS regulations at 45 CFR part 46, **all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied.**

Note: In special circumstances in which the PI asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB will promptly re-review the protocol in accordance with the requirements of subpart C if the PI wants to have the prisoner subject continue to participate in the research.

Prisoner Research Certification

All research involving prisoners conducted or supported by the Department of Health and Human Services (DHHS) must be certified by letter from the IRB to the Office for Human Research Protections (OHRP) that the research was reviewed and approved under the requirements of 45 CFR Part, Subpart C. The letter will indicate which of the four categories of permissible research involving prisoners in 45 CFR 46.306(a)(2) is applicable to the proposed research.

Prisoner-subjects may not be enrolled or involved in a study until the IRB receives a letter from OHRP that acknowledges receipt of the prisoner certification and indicates OHRP's determination regarding the 45 CFR 46.306 category. The IRB will contact the PI upon receipt of OHRP's.

7.4 Research Involving Incapacitated or Decisionally Impaired Subjects

Note: This policy does not apply to the category of research conducted under 21 CFR 50.2. See Exceptions from Informed Consent for Studies Conducted in Emergency Settings

Individuals with diminished autonomy deserve added protection in order to maintain their rights and welfare. For all research involving patients who lack capacity or decisionally-impaired subjects, the capacity of the potential research subject shall be assessed prior to their enrollment and then periodically throughout the course of the research; it will never be presumed that a patient's condition renders him/her incompetent. A legally authorized representative may consent to an individual's participation in research under the appropriate circumstances. Under limited circumstances, as determined by the IRB and based on risk, potential benefit, and the urgency of initiating treatment, approval for consent to be given by a surrogate such as next-of-kin may be granted for a protocol. Approval for the use of surrogate consent will be considered by the IRB for individual protocols in accordance with current Federal and State regulations and guidance.

Definitions

(See OPRR IRB Guidebook, 1993 for references)
http://wayback.archive-it.org/org-745/20150930181805/http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm

Cognitively Impaired: Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Competence: Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. (See also: Incompetence, Incapacity.)
Competence may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. As a designation of legal status, competence or incompetence pertains to an adjudication in court proceedings that a person's abilities are so diminished that his or her decisions or actions (e.g., writing a will) should have no legal effect.

Such adjudications are often determined by inability to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations.

Decisionally Impaired: State of diminished mental capacity that interferes with the ability to make sound, informed judgments regarding medical treatment, or, in the context of research, regarding participation in research studies.

Health Care Proxy: Someone a person appoints to make health care decisions on his/her behalf in the event that he/she becomes unable to make those decisions for him/herself. See New York Health Care Proxy Law.

Incapacity: Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

Incompetence: Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

Institution: A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

Legally Authorized Representative (LAR): An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102). In the case of children, this would be a parent or legal guardian. For adults, a legally authorized representative would have durable power of attorney for health care for the subject or some other court order authorizing him/her to be the legal representative.

Next of kin: The person who is (or persons who are) most closely related to a given person.

There are a number of situations where research subjects may be or may become unable to consent for their own participation in a research protocol. These guidelines include but are not necessarily limited to the following categories of studies:

- **Neurological/Psychiatric studies**, where it is anticipated (but not presumed) that patients may be or become decisionally impaired
- **Clinical protocols** involving medical conditions which often (but not always) render a person physically unconscious or decisionally impaired (i.e. stroke, unstable or serious cardiac conditions, shock, mental status changes due to fever/infections or other reversible conditions, emergency, trauma and ICU research, drug abuse, etc.)
- All other research that may include subjects who might experience fluctuating decisional capacity (due to dementia, emotional distress, etc.)

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur at times of great stress. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally impaired. Some research questions may be answered only by research that involves persons with impaired decision making capacity; precluding this research would contribute to needless suffering.

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired. While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population.

The NIH offers guidance (see Research Involving Individuals With Questionable Capacity to Consent: Points to Consider) to assist IRBs and clinical investigators in their effort to protect participants in research who are, or may be, or may become decisionally impaired, salient points of which are included below:

Conflicting Roles

Potential and actual research participants, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic, and possibly creating confusion among participants and their families.
It is essential that the consent process (including consent documents) clearly indicate differences both between individualized treatment and research and between clinician and clinical investigator.

Assessing Capacity to Consent

Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research

methodology, is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in participants' decision making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision-making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Both IRBs and clinical investigators must keep in mind that decision-making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may require an outside witness to observe the consent process.

Determining Who May Consent for Incapacitated or Decisionally Impaired Subjects

Federal Regulation allows for consent by a legally authorized representative when a research subject is incompetent. For research purposes, a legally authorized representative is the parent or legal guardian of a minor, someone who is explicitly defined in a Health Care Proxy as being able to consent on behalf of the individual to participate in research, or someone who is court-appointed as such.

Note: Under the NY State Health Care Proxy Statute, the act of executing a new proxy automatically voids any prior proxies. Therefore, it is recommended that investigators advise subjects who are signing a “health care proxy for research” to name the same person that they have chosen as a health care proxy for clinical care.

Although Federal and State laws **are not specific**, there are certain circumstances where it may be appropriate to allow a next-of-kin, who may not be a legally authorized representative, to provide consent on behalf of an individual. The determination as to whether or not it is appropriate to accept consent by a next-of-kin is considered for individual protocols by the IRB, and is based on the risk/benefit ratio and the implications of delaying study participation for the amount of time it would take to appoint a legal guardian. The following categories for research involving children, defined in the Federal regulations in 45 CFR 46.404, 405, 406, 407, are used as a guideline by the IRB in making this determination.

- **Research <u>not</u> involving greater than minimal risk**
  Consent should be sought from a legally authorized representative, if reasonably available. If not, a family member, who is aware of the patient's values and believes the subject would have consented to participation may consent to their participation. The relationship between the subject and next-of-kin should be documented in the patient's research/medical record. (The following order should be used when seeking next-of-kin: Spouse, adult children, parents, adult siblings, grandparents, close friend.)
- **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects**
  A legally authorized representative may consent on behalf of an individual for participation in this category of research. A request for approval of surrogate consent (i.e. consent by a family member who is not a legally authorized representative) may be considered by the IRB if the research could not otherwise be carried out, and if exclusion of those individuals without a legally authorized representative denies them access to a potentially beneficial treatment where no other comparable treatment is available, and there is genuine uncertainty about the effectiveness of standard care (i.e. there is clinical equipoise). This may include placebo-controlled trials (when the research is above and beyond standard of care). In order to protect the rights and welfare of the research participant, the use of a surrogate to consent on behalf of another individual in research involving greater than minimal risk will be determined for individual protocols by the IRB after careful consideration of the research protocol and in accordance with current Federal and State regulations.

  The process for determining the appropriate surrogate should be carefully justified by the Investigator for review by the IRB at the time of initial submission and, if granted, documented in the patient's medical/research record.

  - **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**
    Only a legally authorized representative may consent on behalf of an individual for participation in this category of research.
  - **Research not otherwise approvable** which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of humans. Requests under this category of research are extremely rare. Surrogate consent is never acceptable for participation in research falling under this category of research.

In addition to considering the risk/benefit ratio, the IRB will consider the following issues when making a determination regarding surrogate consent for a particular protocol in any/all categories of research:

- Will patient care be compromised by restricting participation to those with legally authorized representatives? (i.e. could a potentially beneficial treatment be denied to patients?)
- Will restricting the use of surrogates significantly affect study accrual for a beneficial study? (i.e. could the study practicably be carried out without the use of surrogates?)
- Is there time to go to court and appoint a guardian?

Comprehension

The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the clinician/investigator. In most cases, it will be the clinician/investigator who is in the ideal position to evaluate the subject's ability to understand the implications of the research and whether the subject is making a rational decision to participate. Likewise, in most studies it is the clinician/investigator who can best make a judgment of the subject's ability to understand and follow the protocol.

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, Q&A sessions for the subject and surrogate and/or family, and waiting periods after the initial discussion before the prospective subject actually enrolls.

There is no universally accepted test or standard for making a determination of comprehension. This process should operate in research studies in much the same manner as the informed consent process in clinical treatment that does not involve research. Investigators may use the Comprehension Evaluation Form to assist them with subject assessment.

For further guidance investigators are encouraged to access the

Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment from The American Journal of Psychiatry, 155:11, November 1998; and

Research Involving Persons with Mental Disorders that May Affect Decision-making Capacity a comprehensive report published by The National Bioethics Advisory Commission (NBAC).

Assent of the Decisionally Impaired

The IRB may determine that the assent of the individual should be sought. For certain populations where the incapacity of the subject may be temporary, the IRB may determine that the consent from the individual is necessary to continue their participation in the study once capacity has been restored.

The IRB may require that a health care proxy be identified for future decision-making on behalf of a particular group of subjects whose capacity is expected to diminish over time. For instance, subjects who are asked to participate in a research study on Alzheimer's disease who are capable of consenting for themselves, but whose capacity is most likely to deteriorate during the course of the research, may be asked to assign a health care proxy for future decision making as a condition of being enrolled or continuing in the study.

All provisions for additional protections (e.g. assent, surrogate consent, capacity assessments, etc.) required by the IRB for the conduct of a particular protocol involving patients who lack capacity or decisionally impaired subjects will be outlined in the individual approval letters for each protocol.

7.5 Additional Special Classes of Subjects

Reference: OPRR IRB Guidebook, 1993

In addition to the vulnerable populations discussed separately (Children, Pregnant Women/Human Fetuses and Neonates, Prisoners, Incompetent/Decisionally Impaired), the IRB shall provide additional protection to other potentially vulnerable populations. This special class of subjects may include, but is not limited to, terminally ill patients, elderly/aged persons, minorities, student/employees/normal volunteers, and economically or educationally disadvantaged persons.

Much of the following information concerning special classes of subjects is taken from the OHRP IRB Guidebook (Chapter VI).

Terminally Ill Patients

Terminally ill patients are those who are deteriorating from a life-threatening disease or condition for which no effective standard treatment exists. It is generally considered unacceptable to ask such persons to participate in research for which alternative, not similarly burdened, populations of subjects exist. Nevertheless, it may often be necessary to involve terminally ill patients in research concerning their disease and its treatment. Further, terminally ill persons should not be excluded from research in which they may want to participate simply because of their status. One can imagine that altruism and a desire to bring good from adversity may well motivate persons suffering from life-threatening illnesses to become involved in biomedical or behavioral research. Still, terminally ill individuals are a vulnerable population of research subjects, and therefore, require additional protection against coercion and undue influence [45 CFR 46.111(b)].

The FDA has a program of Expanded Access that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them (e.g. Treatment INDs, Parallel Track).

In many contexts, research on terminal illness and its treatment requires the involvement of terminally ill patients when alternative populations for study do not exist or when involving alternative populations would be ethically unjustifiable.

Two important reasons for concern regarding research involving terminally ill persons are:

1. They tend to be more vulnerable to coercion or undue influence than healthy adult research subjects; and
2. Research involving the terminally ill is likely to present more than minimal risk.

The risk of coercion and undue influence may be caused by a variety of factors. In addition to the fact that severe illness often affects a person's competence (see Research Involving Incapacitated or Decisionally Impaired Subjects), terminally ill patients may be vulnerable to coercion or undue influence because of a real or perceived belief that participation is necessary to receive continuing care from health professionals or because the receipt of any treatment is perceived as preferable to receiving no treatment. Although terminally ill patients should be protected from an understandable tendency to enroll in research under false hopes, IRBs should not take too protective an attitude toward competent patients simply because they are terminally ill. Some terminally ill patients may find participation in research a satisfying way of imparting some good to others out of their own misfortune.

21

It is important to distinguish between risks that may be justified by anticipated benefits for the research subjects and risks associated with procedures performed purely for research purposes. A particularly difficult issue relating to research involving terminally ill patients arises in connection with the conduct of Phase I drug trials in which the drugs involved are known to be particularly toxic (e.g., a new form of cancer chemotherapy). In some of these studies, any benefit to the subject is, at best, highly unlikely. Despite the "therapeutic intent" (the research physician's intent to provide some benefit to improving the subject's condition) of the investigators to benefit the subject, subjects may in fact experience a decline in health status, no improvements in terms of quality of life, or lengthened life for only a short time. It is extremely important that prospective subjects be clearly informed of the nature and likelihood of the risks and benefits associated with this kind of research. The challenge to the investigator and the IRB is to provide patients with an accurate description of the potential benefits without engendering false hope.

Elderly/Aged Persons

As the American population ages, research on the aging process and conditions and diseases that disproportionately affect the elderly has become increasingly important. The participation of older subjects in research poses several issues for IRBs; primary among them is the question of whether and when the elderly need special protections. IRBs must maintain the balance between the need for protection and the need to provide respect for persons.

While the federal regulations call for additional protections for vulnerable populations, there are no specific regulations governing research with elderly subjects. It is generally agreed, however, that the elderly are, as a group, heterogeneous and not usually in need of special protections, except in two circumstances: cognitive impairment and institutionalization. Under those conditions, the same considerations are applicable as with any other, non-elderly subject in the same circumstances (see Research Involving Incapacitated or Decisionally Impaired Subjects).

There is no age at which prospective subjects should become ineligible to participate in research. Most older people are neither cognitively impaired nor live in institutional settings. Nevertheless, investigators may avoid elderly subjects because of recruiting/retention difficulty, hearing/vision impairment (making the consent process more difficult), memory impairment, etc. However, inclusion of older persons in research is important, and they should have the opportunity to share in the benefits of burdens of research.

In the past, persons in nursing homes or other institutions have been selected as subjects because of their easy accessibility. It is now recognized, however, that conditions in institutional settings increase the chances for coercion and undue influence because of the lack of freedom inherent in such situations. Research in these settings should therefore be avoided, unless the involvement of the institutional population is necessary to the conduct of the research (e.g. the disease or condition is endemic to the institutional setting itself).

Minorities

The inclusion of minorities in research is important, both to ensure that they receive an equal share of the benefits of research and to ensure that they do not bear a disproportionate burden. Most diseases affect all population groups, minority and non-minority alike. For generalizability purposes, investigators must include the widest possible range of population groups. Sometimes, however, minorities are subject to a differential risk. Some research, for example, relates to conditions that specifically affect various minority groups (e.g., sickle cell anemia or Tay Sachs disease), so that involvement of the relevant minority groups is imperative. Other research focuses on characteristics of diseases or effectiveness of therapies in particular populations (e.g., HIV transmission, treatment for hypertension), and may also concern conditions or disorders that disproportionately affect certain racial or ethnic groups. Exclusion or inappropriate representation of these groups, by design or inadvertence, would be unjust. Further, to the extent that participation in research offers direct benefits to the subjects (in HIV research, for example, the receipt of a promising new drug), under-representation of minorities denies them, in a systematic way, the opportunity to benefit. A glaring example of abuse of minority populations' bearing the burden of research can be found in the Tuskegee study, in which a group of African-American men suffering from syphilis were left untreated, despite the availability of penicillin, in order to study the natural course of the disease.

The manner in which subjects are selected bears directly on the problem of inclusion of minorities. The choice of a geographic area for recruitment may affect the representation of racial and ethnic groups in study populations. Also, to the extent that minorities are reliant on public rather than private health care systems, recruitment of subjects from private physicians will tend to exclude minorities and recruitment from public health clinics will tend to over-include them. In fact, recruiting subjects from any health care system assumes that

appropriate subjects have access to and exercise their ability to access a health care system, which may contribute to the homogeneity of the study population. Some writers have suggested that investigators change recruitment strategies so that they recruit subjects through community-based institutions such as churches and neighborhood organizations, rather than solely through health care institutions. In many studies, several institutions collaborate, thereby enrolling subjects from different geographic locations. Such collaborations may also provide a mechanism for ensuring appropriate representation of women and minorities in the study population.

One justification that is offered for research with homogeneous populations is that it is a simpler, less costly way to conduct clinical trials. The more diverse the study population, the larger the subject pool must be (to achieve statistical significance when controlling for differences in race, gender, and ethnicity) and the more variables must be accounted for in analyzing the data. Nonetheless, when homogeneous populations are used, study results are then limited in their applicability to the precise population involved in the study, and may, in fact, hide inaccuracies.

Normal Volunteers

Special concerns surround the involvement of normal (i.e., healthy) persons who volunteer to participate in research. Primarily, the principles involved are **beneficence** and **respect for persons**. In the Belmont Report, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research stated the two general rules that describe beneficent actions as: (1) do not harm; and (2) maximize possible benefits and minimize possible harms. Volunteers for whom no therapeutic benefit can result from participation in research should, therefore, be exposed to risks that are minimized to the greatest extent possible. While the minimization of risks is an important requisite for any research involving human participants, the altruistic motivation of the normal volunteer's agreement to participate (i.e., of contributing to scientific knowledge for the benefit of society) heightens the concern for the risks to which such participants should ethically be exposed.

The principle of **respect for persons** requires that research participants are, where capable of doing so, allowed to act autonomously and to express their right of self-determination. These principles are effectuated through the process of informed consent, which involves providing subjects with all relevant information about the study, including the risks and benefits involved, in clear and simple language, and ensuring that the information is understood and appreciated. Furthermore, the agreement to participate must be **voluntary**; the consent negotiations must be free from elements of coercion or undue inducement to participate. In research involving normal volunteers, particularly where the research involves more than **minimal risk**, IRBs must ensure that any monetary payments to subjects are not so great as to constitute an undue inducement. This issue may be particularly difficult for IRBs to deal with. Since

subjects who volunteer to participate in such studies are usually compensated for their time and discomfort, IRBs should seriously scrutinize the payment schedules to ensure that any compensation offered is commensurate with the time, discomfort, and risk involved. Even so, where a research procedure involves serious discomfort and/or the real, though slight, possibility of serious harm (e.g., studies that involve the insertion and positioning of catheters in veins or the heart), one can easily imagine that the motivation of persons who volunteer to participate may be monetary. IRBs should pay particular attention to the proposed study population and whether it may comprise persons who are likely to be vulnerable to coercion or undue influence, such as persons who are educationally or economically disadvantaged. The federal regulations require that IRBs employ special safeguards under such circumstances [45 CFR 46.111(b)].

One area where normal volunteers are employed in research is in Phase 1 drug trials. The justification for the involvement of normal, healthy subjects is the need for volunteers whose experience with the trial materials is more easily analyzed because of the existence of fewer confounding factors. While Phase 1 trials are the first use of experimental drugs and devices in humans, preliminary studies involving animals provide investigators with data indicating a high likelihood of safe use in humans. Studies have indicated that the risk of injury from participating in Phase 1 studies is small, about the same as the risk of being injured while working as an office secretary [Levine (1982)]. The likelihood of risk, including the availability of animal data, should be scrutinized by IRBs.

Normal volunteers, like students and employees, should be recruited through general announcements or advertisements, rather than through individual solicitations. Personal solicitations increase the likelihood that participation will be the result of undue influence, either because of the relationship between the recruiter and the prospective subject, or methods of communication employed by the recruiter that may act to persuade prospective subjects to participate, thus compromising the voluntariness of the agreement to participate.

Investigators and IRBs should carefully consider what will happen if and when a normal volunteer should become sick or be injured during the research. As with any research involving human subjects, such issues should be clearly spelled out in the informed consent document, and should be reviewed carefully with the prospective subject. For example, subjects should be told: whether any medical treatments will be made available should injury occur and, if so, what they consist of; whom to contact should a research-related injury occur; and that they may discontinue participation at any time without penalty or loss of benefits to which they would otherwise be entitled [45 CFR 46.116(a)(6-8)]. In addition, where appropriate subjects should be told whether they will be dropped from the study in the event of injury or illness, and whether they will be required to pay for treatment of research-related injuries or illness [45 CFR 46(b)(2-3)]. Where illness in healthy volunteers does occur, particularly during a drug study,

investigation by an independent physician may be warranted. [See Fazackerley, Randall, and Pleuvry (1987).]

The issues raised by the involvement of healthy subjects in genetic research is discussed in “Guidebook Chapter 5, Section H, "Human Genetic Research."

Students

Universities, and the association of investigators with them, provide investigators with a ready pool of research subjects: students. Many IRBs have faced the question of whether and in what way students may participate in research. Two questions that have been posed are whether students - medical students, in particular - should be allowed to participate in biomedical research (and whether special protections should be adopted to restrict their participation), and whether participation in research can appropriately be included as a course component for course credit. The latter practice is commonly employed in psychology departments.

The problem with student participation in research conducted at the university is the possibility that their agreement to participate will not be freely given. Students may volunteer to participate out of a belief that doing so will place them in good favor with faculty (e.g., that participating will result in receiving better grades, recommendations, employment, or the like), or that failure to participate will negatively affect their relationship with the investigator or faculty generally (i.e., by seeming "uncooperative," not part of the scientific community). Prohibiting all student participation in research, however, may be an overprotective reaction. An alternative way to protect against coercion is to require that faculty-investigators advertise for subjects generally (e.g., through notices posted in the school or department) rather than recruit individual students directly. As with any research involving a potentially vulnerable subject population, IRBs should pay special attention to the potential for coercion or undue influence and consider ways in which the possibility of exploitation can be reduced or eliminated.

Whether medical students in particular require special protections has been hotly debated. Some universities have either prohibited their participation or severely restricted it to, for instance, research involving minimal risk and minimal interruption of time. Strong arguments have been made against such protections, including claims that as future physicians (and possibly researchers) they may be obliged to participate. Angoff has argued that protecting medical students to a greater degree than protecting other normal volunteers smacks of elitism. Angoff (1985) states, "One may wonder why it is acceptable to ask the masses to accept risk in the name of science but not the very people whose futures are linked to the successful perpetuation of biomedical research" [p. 10]. Nolan (1979), Levine (1984), Angoff (1985), and others have argued that medical students are in a particularly good position to participate in some biomedical research because of their ability to comprehend the procedures involved in studies and evaluate the risks involved, which may not be possible to achieve with other normal

volunteers. Angoff and others have also argued that it is acceptable to pay medical students as one would any research participant.

Requiring participation in research for course credit (or extra credit) is also controversial, though common in the social and behavioral sciences. The justification offered for requiring student participation is educational benefit [Gamble (1982); Cohen (1982)]. Clearly, however, participation of students is seen by faculty-investigators as necessary to the conduct of their research. Grant budgets often do not allow investigators to pay subjects; giving course credit or extra credit is a means of obtaining sufficient participation rates. Again, the issue for IRBs is whether such arrangements for selecting subjects are fair and non-coercive.

Participation in studies might be mandatory or for extra credit. Students in beginning psychology courses, for instance, might be required to serve as subjects for a given number of hours of research or in a given number of research projects. Or they might be given the option of participating for additional grade credit. Several mechanisms have been suggested for diminishing or eliminating the coercive aspect of student participation for course credit that IRBs might find useful. Gamble (1982) describes a departmental guideline for research involving students where extra credit is offered for participation. Students are to be given other options for fulfilling the research component that were comparable in terms of time, effort, and educational benefit: "for example, short papers, special projects, book reports, and brief quizzes on additional readings" [p. 7]. He raises concerns about the comparability of such alternatives with participating in research (e.g., that if they participate in studies, all they have to do is show up and spend the time, but if they choose to write a paper, it gets graded, and if they do extra readings, they have to be tested on them), and concludes that paying student subjects as researchers would any other subject is the only way to protect students' freedom of choice to participate. Cohen (1982) describes a similar policy that seems to meet these concerns. To fulfill the research component, students can either participate in five hours of research, write a brief research paper, or attend faculty research colloquia. The paper is not graded, and students who attend the colloquia have only to show up. If students do choose to participate in studies, the policy seeks to increase the likelihood that participation is freely chosen by requiring: that students be given several studies to choose from and may not be required to volunteer for any particular study; that the studies must not involve more than minimal risk; that students can withdraw from the study at any time without losing the extra credit

Another concern raised by the involvement of students as subjects is confidentiality. As with research involving human subjects generally, IRBs should be aware that research involving the collection of data on sensitive subjects such as mental health, sexual activity, or the use of illicit drugs or alcohol presents risks to subjects of which they should be made aware and from which they

should be protected, to the greatest extent possible. The close environment of the university amplifies this problem.

Where students are likely to be participating in research, IRBs should consider including a student member or consulting with students where appropriate.

Employees

The issues with respect to employees as research subjects are essentially identical to those involving students as research subjects: coercion or undue influence, and confidentiality. As medical students have seemed ideal subjects by biomedical researchers, employees of drug companies have been seen by investigators as ideal subjects in some ways, because of their ability to comprehend the protocol and to understand the importance of the research and compliance with the protocol. Meyers (1979) provides a good summary of the structure of employee volunteer research programs. As student participation raises questions of the ability to exercise free choice because of the possibility that grades or other important factors will be affected by decisions to participate, employee research programs raise the possibility that the decision will affect performance evaluations or job advancement. It may also be difficult to maintain the confidentiality of personal medical information or research data when the subjects are also employees, particularly when the employer is also a medical institution [Meyers (1979)].

PROCEDURES

The IRB shall pay careful attention to research involving such special classes of subjects, and shall consider requiring special procedures for protecting the rights and well-being of these subjects on a case-by-case basis. The IRB shall evaluate the risks and benefits of the research, and ensure that the consent form properly conveys the nature, magnitude and probability of the risks and benefits clearly and accurately. The IRB will pay careful attention to the consent process to ensure that subjects are properly informed and not misled. All of the requirements for Informed Consent must be met. (See Policy 5: Informed Consent). Where necessary, in order to screen subjects for sufficient comprehension and recall of information presented during the consent process, a questionnaire may be required by the IRB, that involves a test of the subject's comprehension and recall of the information presented in the first part. (e.g. for elderly subjects whose comprehension is questionable).

The IRB shall evaluate the study population to ensure proper representation. Research designs that include diverse study populations will be encouraged. Investigators who wish to include a homogeneous study population must provide a justification for doing so. Recruitment methodology will be carefully reviewed to ensure that the appropriate mix of populations will be reached with information about the study. The IRB shall safeguard the rights and welfare of study populations by placing additional safeguards for studies that may present

possible coercion or undue influence on such populations. The consent process will be evaluated to ensure proper communication between researcher and subject, and consent forms will be available in other languages as appropriate to the study population(s). The IRB may require additional safeguards as it deems appropriate.

HIV Populations

The IRB shall follow New York State Law regarding HIV testing. See http://www.health.state.ny.us/nysdoh/phforum/nycrr10.htm

Policy 8: Emergency Use Exemption from Prospective IRB Approval for Use of Unapproved Drugs, Biologics or Devices

A one time "emergency use" of a test article without prospective IRB review is allowed if all of the conditions of 21 CFR 56.102(d) are met, providing that such use is reported to the IRB within 5 working days. The IRB will review and acknowledge the use of this test article. Any subsequent use of the investigational product must have prospective IRB review and approval at a convened meeting. Consistent with HHS regulations, when emergency medical care is initiated without prior IRB review and approval, the patient may not be considered as a research subject.

"Emergency use exemption" refers to the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The FDA exempts from prior IRB review and approval a one-time "emergency use" of a test article [21 CFR 56.104(c)], providing that such use is reported to the IRB within 5 working days, and requires that any subsequent use of the investigational product at the institution have prospective IRB review and approval. Please note: Compassionate use is not synonymous with emergency use. Compassionate use protocols may need prospective IRB approval, if they do not meet the criteria for emergency use exemption.

Definitions

Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below:

Life-threatening: diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life- threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Severely debilitating: diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain the informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

- The subject is confronted by a life-threatening situation necessitating the use of a test article.
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time is not sufficient to obtain consent from the subject's legally authorized representative.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the test article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)]. The FDA must also be notified.

PROCEDURE

A clinician who wishes to use an investigational product in an emergency situation must do the following:

BEFORE USE:

1. Notify the IRB, by telephone or email, as soon as possible about the emergency use of the investigational drug or device. This notification is used to initiate tracking, to assure the investigator files a report with the IRB.
2. The investigator should contact the manufacturer of the drug/device to determine if it can be provided under an existing IND/IDE.
    1. For drugs and biologics, if it is not available through an existing IND, the investigator should contact the FDA to obtain an Emergency IND. FDA contact information can be found at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm.

2. For devices, the developer will need to notify CDRH (301-594-1190) immediately after the device is shipped for use.

Determine whether informed consent is needed from the patient (see Guidance above on Exception from Informed Consent). If informed consent is needed and there is time, work with the IRB to create a consent form for the patient to sign before the test article is used.

AFTER USE:

1. Within 5 working days, a written notification must be sent to the IRB describing the emergency use in that particular individual. The written notification must include:
    1. A letter to the Chairperson of the IRB detailing the patient's medical history, current situation, and a justification for the use of the non-approved treatment modality (drug, device, etc.) The letter must be in sufficient detail to allow the department chairman and the IRB chair or designee to evaluate the treating physician's request.
    2. A copy of the signed consent form, if consent was obtained. If the manufacturer does not have a consent form for use, a clinical consent can be used. The patient must understand the investigational nature of the product being used.
    3. A copy of any correspondence with the manufacturer
    4. A copy of any correspondence with the FDA (including a copy of the Emergency IND, if obtained).
    5. If consent was not obtained because the situation met the requirements outlined above for Exception from Informed Consent Requirement, the investigator must certify in writing how this determination was made. This determination must be reviewed and evaluated in writing, preferably before the emergency use, by a physician who is not otherwise participating in the clinical investigation.
    6. For devices - If an IDE exists, notify the sponsor of the emergency use. If an IDE does not exist, notify FDA of the emergency use (301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures and results.

Once this information is received, the IRB will send a written acknowledgment to the physician, acknowledging the use of this product.

The protocol must be submitted to the IRB for full IRB review if it is anticipated that future patients may require the same treatment in the future. (See also FDA Information Sheets: Emergency Use of an Investigational Drug or Biologic and FDA Device Advice).

Policy 9: Medical Devices

Investigators pursuing the use of an investigational device, the investigational use of an approved device, or the humanitarian use of a device (HUD), as defined in this policy, must obtain IRB approval for its use prior to implementation.

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for *in vitro* diagnosis (IVD) of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the Food and Drug Administration (FDA) informed consent and Institutional Review Board (IRB) regulations [21 CFR parts 50 and 56, respectively]. Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a pre-market notification to FDA.

510(k) devices

FDA reviews pre-market notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendments device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. (The premarket notification requirement for new devices and devices that are significant modifications of already marketed devices is set forth in section 510(k) of the Act). Devices determined by FDA to be "substantially equivalent" are often referred to as "510(k) devices". If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and premarket approval before it can be marketed unless it is reclassified into a lower regulatory class.

Investigational Device Exemption (IDE)

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical

investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR part 812]. An IDE study may not necessarily commence 30 days after an IDE submission to FDA. Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)]. Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "non-significant risk" (NSR). The determination that a device presents a non-significant or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).

The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirements [21 CFR part 812], and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations [21 CFR 812.2(b)]. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, record keeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

The IRB shall make a determination as to whether the device can be classified as SR or NSR. The IRB shall then consider whether or not the study should be approved. In considering whether a study should be approved, the IRB shall use the same criteria it would use in considering approval of any research involving an FDA regulated product [21 CFR 56.111]. Some NSR studies may also qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure [21 CFR 56.110]. FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Frequently Asked Questions About IRB Review Of Medical Devices (FDA Information Sheets, 1998 Update)

1. What is meant by Class I, II and III

The class distinction is made primarily on the level of risk to users/patients and, therefore, the level of FDA oversight needed to ensure that the device is safe and effective as labeled. Generally, but not always, this corresponds to logical risk evaluations.

Class I:	General controls	crutches, band aids
Class II:	Special controls	wheelchairs, tampons
Class III:	PreMarket Approval	heart valves (known to present hazards requiring clinical demonstration of safety and effectiveness) - OR - not enough known about safety or effectiveness to assign to Class I or II

2. What is the difference between marketing approval under a 510(k) and under a PMA?

A 510(k) application demonstrates that a new device is substantially equivalent to another device that is legally on the market without a PMA. If FDA agrees that the new device is substantially equivalent, it can be marketed. Clinical data are not required in most 510(k) applications; however if clinical data are necessary to demonstrate substantial equivalence, the clinical studies need to be conducted in compliance with the requirements of the IDE regulations, IRB review and informed consent (21 CFR parts 812, 56 and 50, respectively).

3. Why should an IRB decide whether a device is non-significant risk (NSR)?

The sponsors (usually the manufacturer of the device) make the initial decision whether a device imparts significant risk (SR) to study subjects or others. If so, the sponsor obtains an Investigational Device Exemption (IDE) from FDA. If the sponsor believes the device does not impart significant risk, IRB approval of a study as an NSR device can be sought. The NSR category was created to avoid delay and expense where the anticipated risk to human subjects did not justify the involvement of FDA. If the IRB agrees that the study is NSR, no submission to or review by FDA is necessary before starting studies in humans. If the IRB

considers the study to be SR, the sponsor must obtain an IDE from FDA before proceeding with clinical studies.

4. What does FDA know about an NSR study?

"There is no requirement to report to FDA when an NSR study starts." The requirements for IRB review, informed consent, adverse event reporting and labeling still apply. In addition, the sponsor should understand that proceeding with an NSR study is at their risk (meaning that the FDA can later disagree) and they may voluntarily seek advice or inform FDA about the decision to proceed without filing an IDE with FDA.

5. How does an IRB decide whether a device is SR or

The IRB uses its best abilities, the information in the regulations and the guidelines, and the risk evaluation provided by the applicant. It can, as always, seek outside assistance. The IRB should have written policies and procedures regarding device review. The information sheet "Significant Risk and Non-Significant Risk Medical Device Studies" provides additional guidance.

6. Does an IRB that reviews medical device studies need written procedures for determining whether the device is SR or NSR?

When the IRB determines that an investigation presented for approval as involving an NSR device actually involves an SR device, 21 CFR 812.66 requires the IRB to so notify the investigator and, where appropriate, the sponsor. 21 CFR 56.108(a)(1) requires the IRB to follow written procedures for conducting its initial review of research and for reporting its findings and actions to the investigator. The procedures followed in determining whether a study is SR or NSR should be included among those written procedures.

7. Does FDA require IRB review of the off-label use of a marketed device?

YES, if the off-label use is part of a research project involving human subjects. NO, if the off-label use is intended to be solely the practice of medicine, i.e., for a physician treating a patient and no research is being done.

8. What is the meaning of exemption in 21 CFR

The exemption applies only to investigations in which 510(k)'d products are being used in accordance with the labeling cleared by FDA. Investigation of an off-label use of a 510(k) product takes it outside this exemption. A device subject to 510(k) remains "investigational" until the 510(k) is cleared by FDA and the investigational use is subject to the requirements of the IDE regulation, informed consent and IRB review (21 CFR 812, 50 and 56, respectively).

9. Must an IRB review a clinical investigation being done after submission of a 510(k)?

YES, if it's research the 21 CFR 50 and 56 regulations apply, and an IRB should review it. A 510(k) allows commercial distribution; it doesn't address research use. A 510(k) application can take time to process during which it remains an investigational product. It cannot be distributed except for investigational use until FDA clears the 510(k) application.

Also see FDA Information Sheets: "Medical Devices," "Significant Risk and Non-significant Risk Medical Device Studies" and "Emergency Use of Unapproved Medical Devices."

Significant Risk And Non-significant Risk Medical Device Studies

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "non-significant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approves the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

SR/NSR Studies and the IRB

The NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the sponsor (in the case of an investigator initiated study, the sponsor is the investigator, who must then present and justify the NSR/SR decision). If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that a SR determination has been made. The study can be conducted as a SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses a SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Two examples follow:

The study of a pacemaker that is a modification of a commercially--available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.
The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.
FDA has the ultimate decision in determining if a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

IRB and Sponsor Responsibilities Following SR/NSR

If the IRB decides the study is Significant

1. IRB Responsibilities:
Notify sponsor and investigator of SR decision
After IDE obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]

2. Sponsor Responsibilities:

Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination;
Study may not begin until FDA approves IDE and IRB approves the study.
Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].
There is no requirement for the sponsor to notify FDA of the SR determination.

If the IRB decides the study is Non-significant Risk:

1. IRB proceeds to review study applying requisite criteria [21 CFR 56.111]. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

The Decision to Approve or Disapprove
Once the SR/NSR decision has been reached, the IRB should consider whether

the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study [21 CFR 56.111]. The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures [21 CFR 56.110].

Examples of NSR/SR Devices

The FDA provides a list of examples to assist sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

Policy 10: Genetic Research and Tissue

All research involving genetic testing, analysis and tissue banking shall be given special consideration with regard to the unique risks presented by such research, and according to current regulation governing such research. See http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm for OHRP guidance on research use of stored data or tissue.

Any research that involves human DNA samples, genetic testing or genetic information is considered genetic research. That includes, but is not limited to, research examining mutations in DNA, research examining differences between traits in individuals with or without a certain disease, and records research involving information derived from previous genetic tests.

In genetic research and research using stored tissue samples there are potential health, societal, emotional and legal issues to consider. Many subjects may be naïve to these issues and it is therefore necessary for the IRB to evaluate the protocols and consent forms for such studies with great care. As this new science develops and laws evolve, it is important to continuously rethink and refine the issues and the way in which they are presented to subjects.

Definitions:

Genetic Research: Research using human DNA samples, genetic testing or genetic information

Genetic Information: Information about an individual or an individual's blood relatives obtained from a genetic test

Genetic tests: The analysis of human DNA, RNA, chromosomes, proteins or other gene products to detect disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.

Genetic Characteristic: A gene, chromosome or alteration thereof that may be tested to determine the existence of or risk for acquiring a disease, disorder, trait, propensity or syndrome, or to identify a blood relative.

Repository (tissue bank): A storage site for collections of human biologic specimens available for study. A repository may reside in one geographic location or may be a virtual collection of biologic specimens from many locations.

Sample: In the context of genetic research, a sample is any human biological material. This includes, but is not limited to: molecular material such as DNA, cells, tissues (blood, bone, muscle, etc.), organs (liver, bladder, heart, etc.), gametes, embryos, fetal tissue, waste (hair, nail clippings, urine, feces, etc.) and other materials of human origin.

Specimen: In reference to a human biological repository, a specimen is the quantity of material stored in the repository, while a sample refers to an aliquot of the specimen supplied to investigators.

Types of studies:

Prospective: studies in which the collection of the new samples is part of the study design.

Retrospective: Studies that utilize previously obtained samples collected for a purpose that is different from that of the current study

Types of Samples: Research samples are grouped into four levels of identification dependent upon the amount of information that is available about the subject from whom the sample was obtained. These levels include:

1. **Unidentified samples (anonymous)**: Samples that are/were obtained and stored without any identification that may link the specimen to a specific subject.
2. **Unlinked samples (anonymized or de-identified)**: Samples that may have been acquired from identified humans subjects, but all identifiers or codes have been removed and destroyed. For unlinked samples, it would be extremely difficult for the investigator, the repository or a third party to identify the person who provided an individual sample. (See de-identified information)
3. **Coded samples**: Samples labeled with a code rather than a name or other personal identifier. When such samples are obtained from a tissue repository, the repository usually retains information that links the code to a particular individual. Using this information, the investigator, the repository or a third party could determine which particular person or small group of identifiable individuals provided the biological specimen. Depending on the nature of the identifiers related to the specimen, the sample may or may not meet the definition of a “limited data set” under HIPAA. The IRB will make that determination and will decide whether the use of the sample, as specified in the protocol, requires a data use agreement, tracking of disclosures, or business associate agreement. See Policy 3: HIPAA.
4. **Identified samples**: Samples collected and supplied to investigators with personal identifiers sufficient to allow person who provided the material to be identified.

10.1 Research Using Prospectively Collected Samples

In general, research involving the prospective collection of coded or identified samples requires subject consent and authorization. Additionally the investigator has the obligation to maintain confidentiality to the extent permitted by law. (This is necessary unless the samples are collected anonymously.)

In addition to the standard elements of consent (see Policy 5: Informed Consent) the consent/authorization forms for such research should clearly indicate:

- What information could result from the research,
- What the implications and limitations are,
- That unexpected findings may result,
- What follow-up information subjects will receive (if any, as many studies are preliminary and results may not be meaningful or validated), and
- Disposition of samples.

If subjects have consented to and authorized storage of samples for future studies, they need to be informed of how long storage will continue and the possibility of storage failure. Subjects should be given the option of being re-contacted to consider use of their samples in future studies. See Informed Consent Guidance on IRB webpage, for a description of sample consent language pertaining to genetic research and tissue banking.

10.2 Retrospective Studies of Existing Samples

When retrospective research is done using anonymous or anonymized samples, consent from subjects is not necessary, since the subjects cannot be individually identified and there is no expected risk to the subject. For research using samples that are identifiable, consent must be obtained. In certain cases the investigator may seek a waiver as detailed in 45 CFR 46.116 (see Policy 5: Informed Consent). If the samples were originally collected for another research study, the initial consent form signed by the subject under which the samples were collected must be consulted to make sure the consent did not contain any information that would disallow subsequent use of the subject's information or specimen.

See . See Informed Consent Guidance on IRB webpage, for a description of sample consent language pertaining to genetic research and tissue banking.

10.3 Tissue Banking

Storing tissue for any additional uses not specified in the consent form signed by the research subject and approved by the IRB is considered tissue banking. HIPAA requires that subjects give explicit authorization for the collection and storage of samples.

Whether or not an activity qualifies as tissue banking depends on the investigator's intent.
For example:

- An investigator may have extra blood drawn and stored as a back up in case a test to which research subjects have already consented needs to be repeated. If he/she destroys the extra samples immediately after test results are complete, this is **not considered tissue banking**, even though tissue samples had been stored.
- If an investigator wants to collect extra samples in case he/she wants to do additional analysis later on that was not included in the original, IRB-approved protocol, that **would be tissue banking** and would require IRB approval and subject consent/authorization. After the additional test is completed, the sample should be destroyed unless the subject has consented otherwise.
- If an investigator wants to collect extra samples to keep on hand for other investigators to use or for use in another study, that **would be tissue banking** and could only be done with IRB approval and subject consent/authorization.

10.4 Disclosure of Results to Subjects

Disclosure of genetic research findings to a research subject, in general, should not occur. Disclosure may be approved in rare circumstances, but only when all of the following apply:

- The research findings are scientifically valid and confirmed (done in a CLIA approved lab);
- The findings have significant implications for the subject's or the public's health; and
- A course of action to ameliorate or treat the subject's or the public's health concerns is readily available.

If results are to be given, subjects should be offered counseling, as appropriate, since results from such research could lead to adverse psychological outcomes, social stigmatization and discrimination. In certain cases subjects should be given the option to determine whether they want to be informed of the results of their testing.

10.5 Protocol/Consent Requirements for Genetic Research or Tissue Banking

In addition to standard submission requirements (see Policy 2: How to Submit a Protocol to the IRB) and general guidelines for informed consent, protocols and consent forms involving genetic research or tissue banking should specifically address the following:

Purpose of Study

- That the sample will be used for genetic

Duration

- How long sample will be stored

Control and Ownership of

- Who owns specimens/materials
- If research could lead to commercially valuable product
- Whether subjects will receive a portion of profits

Subject Access to Genetic Information

- What information subjects are entitled to receive
- If results will not be provided to subjects and why
- If findings are to be disclosed, procedures for doing so (e.g., genetic counseling)
- The point in the research at which the findings will be disclosed (e.g., interim results)
- The policy regarding disclosure of incidental findings

Secondary Use

- Will subsequent investigators be given access to samples with direct or indirect identifiers?
- Will subjects be given option of consenting now to future second use?
- Will subjects be informed that they may be re-contacted? or
- Will subjects be given option to indicate if they are willing to be re-contacted?
- Will subjects have the option of limiting use of sample?

Risks

- **Social Risks**: Breach of confidentiality could impact insurability, employability, reproduction plans, family relationships (including paternity), etc.
- **Psychological Risks**: If information is disclosed, impact of learning results; impact if no effective therapy exists; psychological stress for family members
- **Physical Risks**: Physical risks associated with collecting samples for research purposes and/or for gene therapy procedures
- **Unknown Risks**: Subjects should be told that there may be risks that are presently unknown

Policy Responsibilities of Research Investigators

All investigators must complete Institutionally required training in the protection of human subjects as a prerequisite to being approved to participate in clinical research. The requirement is for all those included as key personnel in the conduct of the research. **See the IRB webpage for recording and pdf files outlining the requirements.**

Key personnel are defined as anyone involved in the development, execution and reporting of the research. This includes all investigators who meet this definition, including research coordinators and lab personnel. Consultants should be listed only when their level of involvement meets this definition of key personnel. Individuals providing technical services and who have no access to individual identifiable information are not considered key personnel.

An individual may not enroll a subject in a research study unless they have complied with the institutional requirement for training in the protection of human subjects **and** are listed as an investigator on the IRB application and approved by the IRB.

The Molloy IRB webpage has a recording and pdf outlining the information about acceptable human subjects training. **Current valid training and credentials of each person named on a protocol MUST be submitted with each IRB submitted package.**

Responsibilities

Ultimately it is the Principal Investigator of a research study at this institution who must accept the following responsibilities:

- Ensuring that individuals involved in the conduct of the study are qualified by education, training, and experience to perform his/her respective task.
- Protecting the rights and welfare of human research subjects. The health and well-being of the individual patient/subject must be the first priority.
- Complying with all Federal, State and Institutional regulations as set forth in the Institutional Policies and Procedures, the FWA, all other pertinent regulatory documents and their amendments.
- Submitting each research activity to the Office of the IRB for determination as to whether it qualifies as exempt or needs expedited or full IRB review.
- Ensuring proper execution of the informed consent process (see Informed Consent), including efforts to ascertain that the subject has comprehended the information in the consent form, as well as retaining all original, signed consent forms. The original consent forms should be retained in a secure file separate from the subject's study records. The most recently approved version of the consent form must be used when consenting a subject.

- Ensuring that any proposed changes in previously approved research activities are submitted to the IRB and that no changes are initiated prior to IRB review and approval, except where necessary to eliminate immediate hazards to the subjects.
- Submitting progress reports, as requested, in a timely fashion (see Progress Reports).
- Complying with all decisions and requirements of the IRB.
- Promptly reporting any serious, unanticipated problems involving risks to subjects or others to the IRB.
- Providing the IRB with accurate and up-to-date information regarding the research.
- Ensuring that additional personnel are added to protocol when necessary in order to include the appropriate expertise for carrying out the protocol.
- Attending or completing education and training sessions offered by the Institution.
- Ensuring that all appropriate key personnel involved in the design, implementation or analysis of the protocol are listed as co-investigators and have been adequately trained in good clinical practice and the protection of human subjects in research (and the responsible conduct of research).

For clinical investigations sponsored by industry, in addition to all of the requirements set forth above:

- complying with all requirements set forth in the clinical protocol and contract. This includes the performance of all protocol-required testing, maintenance of complete and accurate records as per the sponsor's requirements, and complete and timely communication with the sponsor and IRB.

Policy 12: Conflict of Interest/Financial Disclosure Policy

The purpose of this policy is to ensure that the design, conduct, or reporting of research, will not be biased by any conflicting commitment or financial interest of the investigators who are responsible for the research or the IRB members who are charged with its review. The IRB has a process whereby investigators and IRB members must disclose potential conflicts that would reasonably appear to be affected by, or have an effect upon, the research protocol.

Conflict of interest can be defined as any situation in which financial or personal obligations (including related parties) may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research. Financial interests are not prohibited, and not all financial interests cause conflicts of interest or affect the rights and welfare of human subjects. When a potential conflict of interest is disclosed, it will be evaluated by the IRB.

Research investigators, IRB members, IRB staff, and research sponsors may all have possible conflicts of interest. Such conflicts of interest may arise because of the intellectual property involved in many research discoveries or industry-academic partnerships, from financial incentives many pharmaceutical or biotech companies offer researchers for conducting research studies or enrolling subjects, or due to particular relationships within the institution.

A Conflict of Interest Questionnaire Form must be completed by all IRB members (annually) and all investigators (PI and co-investigators) listed on an IRB application (If applicable). In the event a conflict is identified and cannot be eliminated, the IRB may impose such measures as deemed appropriate to manage the conflict.

45 CFR 46.107(e) states that "No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB". To maintain compliance with this requirement, the IRB shall ask any member, including the Chair, with a conflict to leave the room for the discussion and vote. The member may be allowed to answer questions prior to his recusal from the room. Members will not be assigned as a primary reviewer on any protocol with which he has a financial or other conflicting interest.

To avoid a possible conflict of interest, the institutional official (as defined on the FWA) will not serve as a voting member of the IRB.

Definitions:

Investigator: The Principal Investigator, Co-Investigators and all other persons who are responsible for the design, conduct, or reporting of research as described in an application or prospective application made through MC for support of research.

Significant Financial Interest: Anything of monetary value to the Investigator that would reasonably appear to be directly and significantly affected by work externally funded, including but not limited to: salary or other payments or services (e.g. consulting fees or honoraria); equity interests (e.g. stocks, stock options, warrants or other ownership interests); and intellectual property rights (e.g. patents, copyrights and royalties from such rights). Examples include ownership of stock, stock options, or any equity, debt, security, capital holding, salary or other remuneration, or financial consideration, or thing of value for services as an employee, consultant, officer, or board member in:

1. the entity to which the application will be submitted;
2. any entity that owns or has applied for the patent manufacturing of marketing rights to product or procedure involved in, or will predictably result from, the work described in the application.
3. any entity that is known by the Investigator to own or have applied for such rights in any product or procedure that will predictably result from the work described in the application; or
4. any entity that will be a sub-recipient from MC of funding resulting from the application;
5. any entity where the value of financial interests exceeds $10,000 or represents more than a 5% ownership interest for any one enterprise or entity when aggregated for the Investigator and all related parties;
6. any entity from which the Investigator consults or receives other remuneration where the value is greater than $10,000 annually.

Excluded are:

1. salary, royalties or other remuneration paid to an Investigator by MC
2. income from seminars, lectures or teaching engagements sponsored by public or nonprofit entities;
3. income from service on advisory committees or review panels for public or nonprofit entities;
4. financial interests in business enterprises or entities if the value of such interests do not exceed $10,000 and do not represent more than a 5% ownership interest for any one enterprise or entity when aggregated for the Investigator and related parties.
5. consulting or other remuneration from business enterprises or entities if the value does not exceed $10,000 annually.

Related Party: Spouse, domestic partner, & dependent children, siblings, parents, or equivalents by marriage, or other individuals residing in the household.

Reporting of Financial Interests:

The Conflict of Interest Questionnaire for Research contains questions relating to an Investigator's interest in the sponsoring company or any commercial entity that would appear to be affected by the conduct or outcome of the research project. The responses to these questions shall be reviewed by the Director of the IRB or his/her designee. If it determined that a conflict exists, the IRB will determine whether the conflict can be eliminated or managed.

There may be circumstances that warrant a more detailed disclosure to the subjects or additional measures to manage the conflict. The IRB may draft additional disclosure language or prescribe additional appropriate action. These actions may include, among other things, limitations on particular investigator's participation in: study, design, subject recruitment, or data collection; monitoring of study conduct by the IRB or independent observers; or prohibiting the research.

Guidance

The following questions will be considered by the IRB when considering financial interests of parties involved in human subject research, as provided by DHHS:

1) Who is the sponsor, who designed the study, and who is analyzing the data?
2) What are the financial relationships between the researcher and the study sponsor?
3) Is there any compensation that is affected by study outcome?
4) Does the investigator have any proprietary interests in the product including patents, trademarks, copyrights, and licensing arrangements?
5) Does the investigator have an equity interest in the company?
6) Does the investigator receive payments of other sorts from the sponsor (e.g., grants, research equipment, consultant fees, honoraria)
7) Are there any incentive payments?
8) How should financial interests be managed?

Studies sponsored by pharmaceutical or biotech

An institution conducting research that is sponsored by a pharmaceutical or biotech company is usually paid in accordance with the reasonable costs of conducting the study. This may include being paid on a 'per enrolled subject' basis. These funds may be used to support research work in the investigator's laboratory. This, in and of itself, does not constitute a conflict of interest, but the subject has the right to disclosure of this relationship. The IRB may require that a section be added to the consent form as follows:

Investigator Compensation

The principal investigator is being paid by the study sponsor, [company xyz], to conduct this study.

Rarely, there are provisions in some contracts that allow for 'enrollment incentives', also referred to in other terms such as 'competitive enrollment'. This refers to the situation where the institution will be paid more by the sponsor for rapid enrollment or enrollment prior to a certain date. MC does not always prohibit enrollment incentives, but acknowledges that such incentives may also serve to keep the investigator aware of the need for eligible subjects. Further, it is clearly advantageous for research on the etiology, prevention and treatment of diseases to be conducted as quickly as possible, so that results can be assessed, and future research planned. As such, protocols involving enrollment incentives will be assessed by the IRB on a case-by-case basis. Allowance of such incentives will be based on several criteria, including the amount and scheduling of the incentive and the aims of the research. The IRB retains the right to refuse to allow enrollment incentives for a particular protocol. Further, enrollment incentives (monetary or otherwise) meant to provide personal benefit to any investigator (PI or co-investigator) are prohibited.

If any of the investigators on a particular protocol have a significant financial interest or other conflict of interest, the IRB requires, as a condition of approval, that:

a) The IRB determines that the COI can be managed;
b) The investigator cannot be involved in the recruitment or consenting of subjects;
c) The investigator cannot place undue pressure on, or offer incentives to, other investigators to enroll subjects; and
d) A section of the consent form be added that reads:

One or more of the investigators conducting this study has a significant financial (or other) interest in the company supporting the study, which means that they may receive personal financial

benefit from the results obtained. No one with such interest is involved in recruiting or consenting of subjects.

In addition, as with any study, the consent processes for any or all subjects may be witnessed by the IRB or a representative.

Violation of the Policy

In the event a violation of the conflict of interest policy is reported or suspected, such violation shall be immediately reported to the IRB Chairperson and Institutional Official. In the event of investigator violation of the policy, the IRB Chairperson shall determine if any action is necessary to protect human subjects and may take such action, including suspension of IRB approval. The violation shall be reported to the IRB at its next convened meeting for further investigation and determination. Upon investigation and confirmation, the Institutional Official may also take appropriate action, including removal of the Investigator from the affected research.