INSTITUTIONAL REVIEW BOARD

POLICIES AND PROCEDURES MANUAL

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1. MISSION

In the United States, it is current practice for every health care institution and medical facility to have an Institutional Review Board (IRB) to review and approve or disapprove all protocols involving human experimentation for any drugs, surgical techniques or implants and/or devices currently undergoing investigational status and not yet approved by the U.S. Food and Drug Administration (USFDA).

The primary purpose of all IRB's is to safeguard the rights and welfare of humans as research subjects. The IRB examines the plans set forward by an investigator (a physician recognized by the particular manufacturer or distributor as being qualified to undergo this study according to USFDA requirements for documentation) in light of five generally accepted ethical norms: (1) good research design; (2) competent investigators; (3) favorable balance of risk and benefit; (4) informed consent of the subject; and (5) suitable selection of subjects.

The mission of the University Medical Center of Southern Nevada (UMC) Institutional Review Board (IRB) is to protect the rights and welfare of human subjects in research. It is both the responsibility of UMC and the Investigators to ensure the protection of the rights and welfare of human subjects in research. The UMC IRB assures that all of its activities related to human subject research, regardless of funding source, will be guided by the ethical principles described in *The Belmont Report* (i.e., respect for persons, beneficence, and justice), the guidance delineated in the World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects. The UMC IRB is organized and functions in accordance with Parts 50, 54 and 56 of Title 21, Chapter I, Sub-Part A, of the Code of Federal Regulations as amended and currently in effect and Department of Health and Human Services Regulations for the protection of human subjects, 45 CFR 46. The actions of the UMC IRB will also conform to all other applicable federal, State and local laws and regulations.

The UMC IRB is also responsible for reviewing research activities that qualify for exemption from the Common Rule as outlined in 45 CFR 46.104(d) (1-8).

The UMC IRB is responsible for reviewing both funded and non-funded human subject research.

The UMC IRB derives its authority from the Hospital Board of Trustees. The Hospital Board of Trustees has designated the Chief Executive Officer as the Institutional Official for carrying out UMC IRB's research protections program.

2. DUTIES, POWERS, FUNCTIONS

The IRB is to function and operate in accordance with written policies and procedures. The policies and procedures of the IRB are to be reviewed at least annually. Copies of the policies and procedures adopted by the IRB will be made available to investigators, as will revisions, which may be adopted from time to time.

Procedures must be developed, in writing, for:

- Conducting initial and continuing review of research; and, for reporting its findings and actions to the investigator and the institution.
- Determining which projects require review more often than annually and, which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review.
- Ensuring prompt reporting to the IRB of changes in research activity.
- Ensuring appropriate approvals of research; and, that changes in approved research during the period for which IRB approval has already been given may not be initiated without the IRB's review and approval, except where necessary to eliminate apparent immediate hazards to the human subject.
- Ensuring prompt reporting to the IRB and appropriate institutional officials of any unexpected, adverse event. (The investigator, through the sponsor of the study, will report those serious problems to the U.S. Food and Drug Administration (USFDA).

- Reporting to the applicable medical staff department chairperson, the hospital administration and the USFDA of any known serious or continuing non-compliance by the investigator.
- Reviewing research.
- Expedited review procedures.
- Developing criteria for IRB approval of research, including informed consent.
- Reviewing procedures by the institution.
- Suspending or terminating IRB approval of research.
- Reviewing and approving cooperative research.
- Preparing and maintaining adequate documentation pertaining to IRB activities.

The Institutional Review Board (IRB) is established in accordance with the U.S. Federal Food, Drug and Cosmetic Act as amended, the Public Health Service Act as amended, and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) as stated in Chapter I of Title 21 of the Code of Federal Regulations as amended and currently in effect.

The IRB will review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities conducted at University Medical Center of Southern Nevada (UMC.).

The IRB also has the authority to determine whether a drug, drug regimen, procedure or medical device presents a significant risk. No study will be initiated before receiving written approval from the IRB.

Duties of Chairman

It will be the duty of the Chairman to preside at the meetings of the IRB. The Chairman will carry out the Expedited and Facilitated Review procedures.

Duties of Vice Chairman

In the event of the absence of the Chairman, the Vice-Chairman will perform the duties of and have the same authority as the Chairman.

Duties of IRB Coordinator

It will be the duty of the IRB Coordinator to keep a complete record of all business transacted, conduct all necessary correspondence, and send notices of meetings to all members.

3. MEMBERSHIP

Membership must be comprised of at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the UMC. The IRB will be sufficiently qualified through the experience and expertise of its members and the diversity of the members, including consideration of race, gender, cultural background and sensitivity to such issues as community attitudes to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will, therefore, include persons knowledgeable in these areas.

Membership will consist of at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas. In general, at least one (1) unaffiliated member is present that represents the general perspective of participants at convened meetings.

If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or individuals with impaired decision-making ability, consideration will be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, as long as no selection is made to the IRB on the basis of gender. The IRB will annually evaluate, and if necessary, adjust the membership and composition of the IRB to meet regulatory and institutional requirements.

The IRB may not consist entirely of members of one profession. Individuals who are responsible for business development are prohibited from serving as members or ex-officio members on the IRB, and carrying out day to day operations of the review process.

There will be at least one member who is not affiliated with the hospital(s) and is not part of the immediate family of a person who is affiliated with the hospital(s).

There will be two (2) voting members from the University of Nevada, Las Vegas School Of Medicine (UNLV SOM).

Physician members of the IRB must maintain staff privileges on the Medical Staff of University Medical Center of Southern Nevada (UMC.).

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

Membership to the IRB will be by recommendation from present IRB members, the Chief of Staff, hospital administration, or by voluntary request from an interested party.

A Chairman, who is a physician, will be appointed by the Chief Executive Officer of UMC with the advice and approval of the Chief of Staff. The Chairman will appoint a Vice-Chairman, who is a physician. They will serve a three-year term and may be reappointed. The IRB will annually evaluate the performance of the IRB members, chairs, and staff. The IRB will provide feedback to the members, chairs, and staff.

New members will be recommended for appointment to the IRB by the IRB Chair and appointment will be reported in the UMC IRB meeting minutes. They will serve a three-year term and may be reappointed. In the event that the primary IRB member is unable to fulfill their duties as an IRB member, a request for an alternate IRB to be assigned may be submitted to the IRB Chairman for review. If research involving vulnerable populations has certain requirements in regards to membership, potential members are subject to a majority vote of the IRB members.

University Medical Center will be represented by at least one member of its Administrative staff, the hospital legal counsel, and/or the Privacy Officer who can be appointed as a voting member(s).

The IRB Coordinator will be a designated employee of University Medical Center and an ex-officio, non-voting member.

Alternate IRB members

The appointment and function of alternate IRB members is the same as that for primary IRB members, and the alternate's expertise and perspective are comparable to those of the primary IRB member. The IRB roster identifies the primary IRB member(s) for whom each alternate IRB member may substitute. Alternate IRB members may attend any IRB meeting and are encouraged to attend as many meetings as possible. The alternate IRB member will not be counted as a voting IRB member unless the primary IRB member is absent. When an alternate IRB member substitutes for a primary IRB member, the alternate IRB member will receive and review the same materials prior to the IRB meeting that the primary

IRB member received or would have received. The IRB minutes will document when an alternate member replaces a primary IRB member.

4. SIGNATORY AUTHORITY

The UMC IRB Chair, Vice-Chair and designated reviewers are authorized to sign any and all documents in connection with the review and approval of research projects. The UMC IRB allows the IRB Chair, Vice-Chairman and designated reviewers to utilize the use of signature stamps and electronic signatures. In all cases individuals must sign/electronically sign/stamp their own name and no other. The IRB Chair, Vice-Chair, or designated reviewer can sign/electronically sign/stamp the following items:

- Results of Reviews, Actions and Decisions

The IRB Coordinator may sign routine internal correspondence that provides information concerning the review of research protocols by the IRB or staff which do not imply or appear to imply approval. The UMC IRB allows the IRB Coordinator to utilize the use of a signature stamp. In all cases individuals must sign/stamp their own name and no other. The IRB Coordinator may sign/stamp the following items:

- Routine External Correspondence
- Any letters, memos or emails between the IRB, and/or members of the research community that provide information concerning the review of research protocols by the IRB staff which do not imply or appear to imply approval of this activity
- Correspondence with External Agencies
- Any letters, memos or emails sent to agencies of the federal government, funding agencies (whether private or public) or their agents
- Decisions Made by Chair or Vice-Chair

All signature stamps will be kept in a locked cabinet in the IRB office. Individuals must sign/stamp their own name and no other.

5. MEETINGS OF THE IRB

Scheduled Meetings
The IRB will meet at least six (6) times per year, and may meet monthly or at other times as deemed necessary.

Special Meetings
Special meetings may be held under any of the following circumstances:

The Chairman of the IRB determines that a special meeting is necessary; two or more members of the IRB request that the Chairman call a special meeting; An IRB member has reported to the hospitals administrative staff that there is reason to believe an investigator is:

- Not following the approved protocol; and/or
- Not following the approved informed consent procedures; and/or
- Not reporting unexpected serious adverse events consequences.

Notice of Meeting Preparation
Notice of meetings will be in writing and will include the date, time and location of the meeting. Notices will be given in a timely manner to allow meaningful review of the subject matter.

Unless the Chairman determines that an emergency exists, the meetings will not be convened on less than one (1) weeks' notice. If the Chairman determines that an emergency exists, any materials pertaining to the subject matter of the meeting will be made available to the IRB members for review prior to or at the meeting.

If a protocol for a new study is to be discussed at the meeting, the following materials will be available in the Medical Staff Services Department prior to the meeting:

- A completed IRB Application;
- The protocol to be discussed;
- The Informed Consent Form the investigator proposes to use; and
- Other information, if any, provided by the investigator

When ongoing research or investigation is to be reviewed at the meeting, the continuing review progress reports will be available for evaluation.

Quorum

A quorum is defined in 21 CFR 56.107(a), 21 CFR 56.108c and 45 CFR 46.108(b) as a convened meeting at which a majority of the IRB members are present, including at least one member whose primary concerns are in non-scientific areas and one member whose primary concerns are in scientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

No meeting of the IRB will be convened for the purpose of approving research or investigation or reviewing an ongoing research study or investigation unless a quorum is present. Approval is by at least five (5) members present and voting, to include one member whose primary concerns are in non-scientific areas. Should the quorum fail during a meeting, (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a non-scientist member); the IRB may not take further actions or votes unless the quorum can be restored.

6. CONFLICT OF INTEREST

IRB Member Conflict of Interest

Before any research or investigation is reviewed, each member of the IRB will disclose any relationship with the sponsor and/or investigator. No member will participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

No member of the IRB will participate in any review of any research or investigation in which the member is involved as described below. This includes non-financial and financial interests of the member. Examples of this include but are not limited to:

- involvement in the design, conduct, or reporting of the research
- involvement of immediate family in the design, conduct, or reporting of the research
- financial interest related to the members themselves or immediate family members of investigators in the research.

When, for any reason, it appears that there is a conflict of interest by way of an IRB member's associations or those of his immediate family, the member will inform the IRB and disqualify himself/herself from participation in the deliberations and voting. Immediate family is defined as one's spouse, children, siblings, or parents.

If information comes to the attention of the IRB indicating a potential or actual conflict of interest, it will be explored. A majority of those present at a meeting where quorum requirements are satisfied may determine that a member has a conflict of interest and excuse that member from deliberations and voting.

Once a member or consultant has been identified with a conflict of interest, they will:

- Be excluded from discussion except to provide information requested by the IRB
- Abstain from voting

This applies to all research protocols reviewed by the IRB, regardless of whether the project is exempt or considered during expedited or continuing review or during a review by the convened IRB.

The standard that should guide decisions about conflicting interests whether an independent observer could reasonably question whether the individual's actions or decisions would be based on factors other than the rights, welfare, and safety of the subjects.
A conflicting interest generally includes participation in or supervision of a project, financial interests, a personal relationship, or a fiduciary relationship, all as defined below. Certain other types of interests may also be conflicting interests, as explained below. A conflicting interest may arise because of an interest that the IRB member or his/her immediate family, has; the aggregate interest of the IRB member or his/her family, is considered.

- "Immediate Family" means the IRB member's spouse or domestic partner and dependent children as defined by IRS.
- "Participation in a project" means that IRB member or consultant is listed as an investigator on the protocol or is a member of the research team.

Investigator Conflict of Interest

An investigator will report any financial interests or any other association with a company or group sponsoring a research protocol. If a financial conflict of interest is present, a conflict management plan will be developed and forwarded to the IRB for review and approval. The IRB Chair or Vice-Chair will then determine if the conflict adversely affects the protection of human subjects and if the management plan is adequate. The IRB application asks protocol-specific questions regarding conflict of interest for the investigators. As part of its review process, the IRB will make a determination as to whether the conflict adversely affects the protection of human subjects. If a conflict of interest exists, final IRB approval cannot be given until an approved conflict management plan that adequately protects the human subjects in the protocol is in place.

The Investigator must complete the "**Conflict of Interest Disclosure Statement"** form and submit it to the IRB with all new protocol applications.

If the conflict of interest status of an investigator changes during the course of a study, the individual is required to notify the UMC IRB in writing, within 10 working days of the change. The IRB will then review the change as a modification to the protocol.

At the time of Continuing Review, the investigator will be asked if there have been any changes in the conflict of interest status relating to the research. The IRB will review conflict of interest as part of its continuing review.

Notification will appear in the Informed Consent Form if the sponsor is paying the Investigator or his/her institution to conduct the study and that the amount of this payment is sufficient to cover the Investigator's and/or institution's expenses to perform the study, and does provide personal financial benefit to the Investigator and/or his/her institution.

7. FEES TO REVIEW SPONSORED RESEARCH PROTOCOLS

In 1999, a fee was implemented for new industry-sponsored protocols being reviewed by the UMC IRB and has since been updated to include fees relating to expedited review, continuing review and requests for the IRB to hold a special meeting prior to the next IRB meeting. The fee structure is updated from time to time to match what other institutions are charging around the country. These fees apply to all industry-funded human subjects' research conducted at UMC. Excluded from the IRB review fee are human research protocols funded by federal or state agencies, non-profit foundations or by departments/divisions/centers within UMC. The Principal Investigator is responsible for including these fees in their budget with the industry sponsor. The IRB review fees are assessments for a portion of the real costs associated with protocol review by the IRB. Invoices for the IRB review fee are generated and submitted to sponsors once a protocol has been submitted to the IRB for review. The actual costs of the review process are still incurred if subjects are never enrolled, the study terminates before milestones are met, expenditures exceed revenue, or a contract is never finalized. The invoice is therefore due and payable upon receipt. The UMC IRB may waive IRB review fees at its discretion. The UMC IRB does not assess fees for unfunded projects, medical records research that is not industry sponsored, projects that qualify as Exempt Review, reporting of non-compliance, potential unanticipated problems or adverse events and emergency situations requiring IRB review are generally not assessed a fee. Fees may not be waived because a sponsor has previously paid a fee to a regional IRB for review.

IRB funds will be monitored and held in the same manner as the Medical Executive Committee (MEC) funds. All monies will be collected by the IRB Coordinator and approved by the IRB Chairman or Vice Chairman for disbursement. Use of IRB Funds will then be reported to the next regularly scheduled IRB meeting and reported to the MEC in the IRB minutes. The IRB funds will be utilized for educational conferences, seminars, educational materials, subscriptions, software, memberships and travel expenses associated with conference/seminar attendance. IRB funds may be approved and disbursed for other expenses at the discretion of the IRB Chairman or Vice-Chairman upon request. Requests for the use of IRB funds will be considered for any IRB Member, IRB Community Member, the Medical Staff Manager, IRB Coordinator, or individuals who actively participate in UMC's research program.

8. IRB REVIEW OF PROPOSED RESEARCH

The investigational protocol and all other related IRB submission information will be available in the IRB Office for review by members of the IRB at least thirty (30) days prior to the meeting date. THE IRB AGENDA WILL BE CLOSED AFTER A MAXIMUM OF FOUR (4) IRB INITIAL SUBMISSIONS ARE RECEIVED. This will be based on a first-come-first-served basis. Any initial submissions after the first four (4) will be presented at the next regularly scheduled IRB meeting.

The IRB will request that the Principal Investigator or Co-Investigator involved in the proposed study be present at the meeting to describe the project, to answer any questions that may arise, and to discuss any changes in the protocol/informed consent that the members may determine are necessary.

FAILURE TO PROVIDE THE INFORMATION/DOCUMENTS STATED IN THE CONTINGENT APPROVAL LETTER WITHIN 30 DAYS FROM THE DATE OF THE LETTER, WILL RESULT IN THE PROTOCOL BEING DISREGARDED AND A NEW SUBMISSION WILL BE REQUIRED.

If it is not readily apparent from the protocol how subjects are to be selected and what inducements will be offered to encourage them to participate in said research or investigation, the investigator will provide that information to the IRB.

When additional information is deemed necessary, the IRB can request technical assistance from other professionals including, but not limited to, members of the medical staff and its committees. If the IRB reviews research that involves participants likely to be vulnerable, at least one IRB member should be knowledgeable about the applicable vulnerable population. If it is determined that there is not at least one person on the IRB with appropriate scientific or scholarly

expertise to conduct an in-depth review of the protocol, the IRB will defer the review to another meeting or obtain consultation regarding the protocol.

In cases of detailed and lengthy protocol applications, the Chairman may decide to appoint subcommittees to more closely review individual components. Subcommittees may be appointed by the Chairman to complete detailed reviews and to suggest recommendations. The subcommittees will report their findings, in summary, to the IRB members at a regular meeting.

The IRB may request that the investigator obtain additional information from the sponsor.

9. CRITERIA FOR IRB APPROVAL

Prior to approval, the IRB must determine that the following criteria have been met:

- The Principal Investigator has provided:
  - Information regarding the purposes of the research;
  - Scientific and/or scholarly rationale;
  - Procedures to be performed;
  - Setting in which the research will be conducted;
  - Whether prospective participants will include vulnerable populations
  - The selection (inclusion/exclusion) criteria
  - Subject recruitment and enrollment procedures
  - The amount and timing of payments to participants
  - The possible influence that could occur if payment is given to participants
  - Description of the procedures being performed already for diagnostic or treatment purposes; -
  - The risk and potential benefits of the research;
- Risks to subjects are minimized:
  - By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
  - By using procedures already being performed on the subjects for diagnostic or treatment purposes.

(The IRB reserves the right to require documentation of Sponsor Standard Operating Procedures and other related documents before approval of a protocol is granted.)

- The research plan makes adequate provisions to protect the privacy interests of participants. The application must include a description of provisions to protect the privacy interests of participants.
- The research plan must make adequate provisions to maintain the confidentiality of data. These provisions should be included in the application.
- When approving research, the IRB determines when research requires that adequate provisions for monitoring data are in place to ensure the safety of participants, which includes a review of the protocols more often than annually.
- Applications include a description of the consent process including:
  - A copy of the proposed consent document
  - The person who will conduct the consent interview
  - The person who will provide consent of permission
  - Any waiting period between informing the prospective participant and obtaining consent
  - Steps taken to minimize the possibility of coercion or undue influence
  - The language used by those obtaining consent
  - The language understood by the prospective participant or the legally authorized representative

- The information to be communicated to the prospective participant or the legally authorized representative

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

Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. It should be particularly cognizant of the special problems of research involving vulnerable populations such as children, prisoners, pregnant women, handicapped or individuals with impaired decision-making ability, or economically or educationally disadvantaged persons.

Additional safeguards have been included in the study to protect the rights and welfare of subjects if some or all of the subjects (as identified in the paragraph above) are likely to be vulnerable to coercion or undue influence.

An informed consent is obtained from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by Part 20.

An informed consent is appropriately documented in accordance with and to the extent required by Section 20.27.

The research plan, where appropriate, makes adequate provision for monitoring the data collected to safeguard the safety of subjects. For multi-site research, adequate information should be provided for the IRB to be able to evaluate whether the management of information for the protection of the participants is sufficient. This should include existing unanticipated problems involving risks to participants or others, interim results, and protocol modifications.

There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data by applying and following current HIPAA regulations.

The investigator will provide explanation of the protocol and an informed consent in the patient's native language if the patient does not adequately understand English. ICF's translated into a foreign language must be made by a certified translation service or individual who has met requirements as a certified translator.

The IRB will consider whether investigators have the resources necessary to protect participants which include, but are not limited to:

- Adequate time for the researchers to conduct and complete the research
- Adequate number of qualified staff
- Adequate facilities
- Access to a population that will allow recruitment of the necessary number of participants
- Availability of medical or psychosocial resources that participants may need as a consequence of the research.

10. IRB ACTIONS

- Protocols reviewed during the course of business will be assigned to one of the following categories:
  Approved: This action means that the clinical investigation has been reviewed and may be conducted at this institution within the constraints set forth by the IRB and other institutional and federal requirements. A letter of approval will be sent to the investigator, along with a copy of the approved Informed Consent form with the date of expiration noted on each page.

- Approved-Contingent Upon Required Modifications: This action means that the Board has identified certain areas of the protocol or informed consent that require modifications which will make the protocol or informed consent acceptable (for example, the IRB may recommend that a specific sentence be added to the informed consent).
- When all required modifications have been completed and the revised documents returned to the Chairman, the Chairman may approve the protocol as directed at the previous meeting without further consulting the full IRB. A letter of approval will then be sent to the Investigator, along with a copy of the approved informed consent form with the date of approval noted on each page.
- Deferred: Any member of the IRB may move to defer/table a protocol. A motion to defer/table must include a plan for subsequent action. There are three types of plans for subsequent action:
    - The investigator may be called upon to supplement the information contained in the protocol. This may include a request for additional information from the sponsor;
    - The IRB may agree that it has adequate information, but there are still irreconcilable differences of opinion. In this case, a subcommittee is appointed by the Chairman for purposes of discussing the problems further and, if necessary, negotiating some compromises. After the subcommittee has completed its business, it reports back to a meeting of the full IRB.
    - The IRB may feel that it does not have sufficient expertise to assess some aspects of the protocol. One or more members will be appointed to find a suitable consultant who will present additional information to the full IRB at a subsequent regular meeting.
- Disapproved: The IRB may disapprove a research protocol. When this occurs, a statement of the reasons for the disapproval will be given to the investigator along with the notice of such disapproval. Such information should also be communicated to the sponsor where deemed appropriate.
    - Disapproval is accomplished de facto when requirements for revision are stipulated by the IRB, which the investigator does not accept. If the required modifications have not been received by the following IRB meeting, the Chairman will forward a letter requesting the investigator to provide the modified documents or withdraw the protocol from consideration before the next meeting. If no response is received, the protocol is automatically withdrawn from consideration.

Per CFR 45 Part 46.112, research that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Reporting To Investigator & Sponsor
Approval or disapproval of a proposed research project or investigation and any required modifications of an approved research or investigation will be communicated to the investigator in writing.

Where the IRB disapproves a research activity or investigation, a statement of the reasons for the disapproval will be given along with the notice of such disapproval. Such information should also be communicated to the sponsor where deemed appropriate.

11. EXPEDITED REVIEW (45 CFR 46.110; 21 CFR 56.110)

The IRB may use the expedited review procedure to review either or both of the following:

- Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,
- Minor changes in previously approved research during the period for which approval is authorized; or
- Research for which limited IRB review is a condition of exemption under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

Expedited Reviews are approved by the IRB Chair, Vice-Chair, or a designated reviewer.

Minor Modifications to Previously Approved Research
An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized [45 CFR 46.110; 63 FR 61 60364-60367, November 9, 1998 and 63 FR 60353-60356, November 9, 1998; 21 CFR 56.110(b)]. There is no deadline to submit an expedited review.

A minor modification is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

- the level of risks to subjects
- the research design or methodology
- the number of subjects enrolled in the research (no greater than 10% of the total requested)
- the qualifications of the research team;
- the facilities available to support safe conduct of the research; or
- any other part of the research that would otherwise warrant review of the proposed changes by the full board.

Examples of minor modifications include, but are not limited to:

- Protocol revisions that entail no more than minimal risk.
- Changes to the informed consent documents that do not affect the rights and welfare of study subjects, or do not involve increased risk, or significant changes in the study procedures.
- Changes in research personnel or contact information.

The reviewer(s) and the entire IRB will have access to the entire study file including the following documents:

- Modification of Protocol
- Revised/updated *Protocol*
- Revised/updated consent, parental permission, assent documents (if applicable)
- Additional recruitment materials (e.g., letter of invitation, recruitment script, and flyer)
- New HIPAA authorization form, waiver of authorization form
- New surveys, questionnaires, interview questions, and assessment instruments
- Any other relevant documents
- Grant information
- If there are any changes to research personnel:
    - Verification of current human research protection training for all new research personnel

Minor Administrative Changes
Some minor administrative changes may be approved by qualified IRB staff who do not serve as Designated Reviewers (a larger scope of modifications can be approved by IRB staff who are also Designated Reviewers and IRB Members; this scope is documented in a separate Standard Operating Procedure). These changes are exclusively limited to the following:

1. Change of contact information
2. Addition or deletion of junior level personnel (not co-investigator, principal investigators)
3. Addition of co-investigator
4. Addition or removal of co-investigator for minimal risk studies
5. Title change if not accompanied by a change in the study
6. Corrections of typographical errors
7. Reformatting of unchanged text
8. Errors in completion of the IRB application, as confirmed with study staff as appropriate
9. Removal of study sites that were never activated
10. Change of funding status from “pending” to “approved” (addition of grant application should be sent to Designated Reviewer)

11. Other changes that involve only logistical or administrative aspects of the study (e.g., change of monitor), after consultation with IRB staff Designated Reviewer(s).

When reviewing research under an expedited review procedure, the IRB Chair, or designated experienced IRB member(s) reviewers, should receive and review all documentation that would normally be submitted for a full-board review, including the complete protocol, and determine the regulatory criteria for use of such a review procedure. A designee is an IRB member recognized by the IRB Chair, who has a minimum of 6 months' experience on the IRB. An experienced member is one who has demonstrated a consistent and comprehensive pattern of review of assigned protocols as an IRB member and has demonstrated a dedication to the protection of human subjects with his or her actions and comments.

The regulatory criteria determined by the reviewers will be documented in the agenda and minutes of the next scheduled meeting after the expedited review application is approved. Reviewers should use the required criteria for approval of research to approve research using the expedited procedure.

The reviewer of the research will ensure that the research meets the applicability criteria and represents one or more approvable categories of research. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in 45 CFR 46.108.

When a proposed change in the research study is major or the IRB requests substantive clarification or modification, the full IRB must review and approve the proposed changes and protocol at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subject. In this case the IRB will be promptly informed of the change following its implementation and should review the change in the study to determine that it is, in fact, consistent with ensuring the continued welfare of the research subjects.

Categories Eligible for Expedited Review (63 FR 60364-60367, November 9, 1998)
The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- Unless an IRB determines otherwise, continuing review of research is not required for research eligible for and approved by expedited review in accordance with 46.109(f)(1)(i).

Research Categories one (1) through seven (7) pertain to both initial and continuing IRB review:(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
(a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
(b) from other adults and children[1], 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. [[1]Children are defined in the DHHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."][45 CFR 46.402(a)]

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

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]

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

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; *or*
(b) where no subjects have been enrolled and no additional risks have been identified; *or*
(c) where the remaining research activities are limited to data analysis.
[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure. For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

(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.
[Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (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. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.]
All members of the IRB will be apprised of all expedited review approvals and contingent approvals by means of the agenda for the next scheduled meeting under the appropriate section. Copies of the expedited review approvals will be made available for any optional review at the request of any IRB member.

12. NCI CIRB INDEPENDENT MODEL

The NCI CIRB Initiative is a cooperative venture with FWA institutions that is intended to create a more effective and efficient mechanism for IRB oversight of NCI-sponsored Cooperative Group clinical trials. Specifically, the NCI CIRB is designed 1) to improve access to NCI-sponsored Cooperative Group clinical trials for potential study participants and their physicians by enabling rapid approval of clinical trials through the use of the CIRB review process; 2) to enhance the protection of study participants by providing consistent expert IRB review at the national level; and 3) to reduce the administrative burden for local IRBs and research staff. Under an Authorization Agreement and Division of Responsibilities document with the NCI CIRB, the CIRB is the sole IRB of record responsible for the review of cooperative group oncology studies performed at participating institutions.

In such cases where University Medical Center of Southern Nevada has a Consortium Agreement with an independent signatory of the NCI CIRB the independent signatory will add the University Medical Center of Southern Nevada to their NCI CIRB Affiliate Agreement. NCI CIRB will serve as the IRB of record for the University Medical Center of Southern Nevada for NCI-sponsored Cooperative Group Human Subjects Research under that Affiliation Agreement. The CIRB does not approve the HIPAA Authorization language as it does not function as a Privacy Board, as such, the UMC IRB will provide separate approved HIPAA Authorization language.

In cases where University Medical Center of Southern Nevada does ***not*** have a Consortium Agreement with an independent signatory of the NCI CIRB the following will apply:

Definitions:
Signatory Institution: A Signatory Institution is the institution that signs the Authorization Agreement and Division of Responsibilities document and has a direct relationship with the CIRB. The responsibilities of the Signatory Institution are listed on the Authorization Agreement and Division of Responsibilities document.

Signatory Institution Principal Investigator: The Signatory Institution Principal Investigator is an investigator at the Signatory Institution who is a member of the group coordinating the study and therefore is able to open studies with the CIRB. The Signatory Institution Principal Investigator is responsible for the research at their institution and all research activities conducted by the research staff (including any research activity at Component or Affiliate Institutions) for all studies opened in their name. Signatory Institution Principal Investigators must be "employed by" or "have a relationship with" the Signatory Institution to be eligible to open studies.

Component Institution: A Component Institution is defined by the NCI CIRB as follows:

a. The Component Institution usually operates under a different name than the Signatory Institution but the Signatory Institution has legal authority over the Component Institution;
b. The FWA number for the Component Institution is the same as the Signatory Institution;
c. The local context considerations of the Component Institution are the same as the Signatory Institution;
d. The boilerplate language and institutional requirements of the Component Institution are the same as the Signatory Institution; and
e. The conduct of research at the Component Institution is monitored by the same office as the Signatory Institution.

Affiliate Institution: An Affiliate Institution is defined by the CIRB as follows:

a. The local context considerations of the Affiliate Institution are the same as the Signatory Institution;
b. The boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution; and
c. The conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution.

Signatory Institution Primary Contact: The Signatory Institution Primary Contact(s) is the person(s) who acts as the point of contact for the CIRB should the CIRB have any questions about the research being conducted at the Signatory Institution, Component Institution(s), or Affiliate Institution(s). The Signatory Institution Primary Contact(s) receives or is copied on all correspondence from the CIRB to the Signatory Institution and the Signatory Institution Principal Investigator(s). This individual is also responsible for the submission of Annual Signatory Institution Worksheet About Local Context, and may also assist with other Worksheet completion. The IRB Coordinator will serve as the Signatory Institution Primary Contact.

Boilerplate Language: Boilerplate language is the information added by the Signatory Institution Principal Investigator to the CIRB-approved consent form after the CIRB approves it. Boilerplate language provides information that is institution-specific and addresses local context considerations for the Signatory Institution and its Component and Affiliate Institutions. This information may include contact information for the Signatory Institution Principal Investigator, institution-specific injury language, institution-specific pregnancy language, and other institution-specific information. Updates to boilerplate language must also receive CIRB approval prior to implementation.

In the independent model, the CIRB is the sole IRB of Record responsible for both study reviews as well as review of local context consideration for enrolled institutions. The primary reason for this model change is to more clearly define the responsibilities of Signatory Institution and the CIRB.

The UMC IRB maintains responsibilities for local oversight of performance of CIRB-approved studies. These responsibilities involve ensuring the safe and appropriate performance of the research at its affiliated institutions including, but not limited to, ensuring the initial and ongoing qualifications of investigators and research staff; overseeing the conduct of the research; monitoring protocol compliance, maintaining compliance with state, local or institutional requirements related to the protection of human subjects; providing a mechanism to receive and address concerns from local study participants and others about the conduct of the research; and investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that seems to rise to the level of an unanticipated problem and/or serious or continuing noncompliance.

In accordance with:
National Cancer Institute Central Institutional Review Board Independent Model Information and the NCI CIRB Standard Operating Procedures

Compliance with this policy also requires compliance with state or local laws and regulations that provide additional protections for human research subjects

Division of Responsibilities between the NCI CIRB and UMC

The responsibilities of the NCI CIRB are to:

1) Maintain an NCI CIRB membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56 and provides special expertise as needed to adequately assess all aspects of each study; a) post the roster of NCI CIRB membership on the public side of NCI CIRB website;

2) Conduct initial, amendment, and continuing review of studies as well as review of any other study-specific documents submitted by the Study Chair to the NCI CIRB;

3) Conduct review of local context considerations: as outlined in the following Worksheets: The Annual Signatory Institution Worksheet About Local Context for NCI CIRB Review, the Annual Principal Investigator Worksheet About Local Context, and the Study-Specific Worksheet About Local Context;

4) Conduct review of potential unanticipated problems and/or serious or continuing noncompliance when the Signatory Institution or other entity reports an incident, experience, or outcome to the CIRB. This review includes the following step: report any unanticipated problem and/or serious or continuing noncompliance determination to OHRP, the FDA, and the NCI Signatory Official;

5) Conduct review of individual Adverse Event Reports for studies without a Data and Safety Monitoring Board (DSMB) or equivalent monitoring body;

6) Post all study-specific documents related to CIRB reviews to the restricted access side of the CIRB website; Notify research staff and institutional designees of all CIRB actions, per written procedures, via institution-specific correspondence, broadcast emails, and access to the restricted area of the CIRB website;

7) Notify the Signatory Institution immediately if there is ever a suspension or restriction of the CIRB's authorization to review a study; and

8) Post the NCI CIRB Standard Operating Procedures on the public side of the CIRB website.

The responsibilities of the Signatory Institution are to:

1) Comply with the NCI CIRB's requirements and directives;

2) Report to the NCI CIRB the names of any Component or Affiliate Institutions that rely on the Signatory Institution's IRB.
    a) Component Institutions are defined by the NCI CIRB as meeting all of the following criteria:
        - the Component Institution operates under a different name than the Signatory Institution, but the Signatory Institution has legal authority for the Component Institution;
        - the FWA number for the Component Institution is the same as the Signatory Institution;
        - the local context considerations of the Component Institution are the same as the Signatory Institution. Local context considerations are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and

- the conduct of research at the Component Institution is monitored by the same office as the Signatory Institution.

b) Affiliate Institutions are defined by the NCI CIRB as meeting all of the following criteria:

- the local context considerations of the Affiliate Institution are the same as the Signatory Institution. Local context considerations are reported by the Signatory in the Annual Institution Worksheet About Local Context;
- the boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution. The boilerplate language and institutional requirements are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and
- the conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution.

3) Ensure the safe and appropriate performance of the research at the Signatory Institution and all Components and Affiliates. This includes, but is not limited to:

a. ensuring the initial and ongoing qualifications of investigators and research staff;
b. overseeing the conduct of the research;
c. monitoring protocol compliance;
d. maintain compliance with state, local or institutional requirements related to the protection of human subjects;
e. providing a mechanism to receive and address concerns from local study participants and others about the conduct of the research;
f. investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that seems to rise to the level of an unanticipated problem and/or serious or continuing noncompliance, the institution must provide a plan to manage the incident, experience, or outcome, including measures to prevent similar occurrences;

NOTE: As part of ensuring safe and appropriate performance of research the Signatory Institution has the authority to observe any aspect of the research process including observing the consent process. The CIRB retains the authority to direct this to be done when necessary.

4) Provide updates in a timely manner to the NCI CIRB whenever a Signatory Institution Principal Investigator is no longer the responsible party for a study under the purview of the NCI CIRB;

5) Notify the NCI CIRB when a regulatory deficiency has been cited on an audit that occurred during the time that the NCI CIRB was responsible for study review;

6) Complete and submit the Annual Institution Worksheet About Local Context, the Annual Investigator Worksheet About Local Context, and any other worksheets/forms required by the NCI CIRB for participation;

7) Decide on a study-by-study basis whether to open the study through the NCI CIRB or to conduct its own local IRB full Board review. Indicate the decision to open a study through the NCI CIRB by submitting a Study – Specific Worksheet About Local Context;

8) In the local consent form:

a) incorporate NCI CIRB-approved boilerplate language into the NCI CIRB- approved model consent form;

NOTE: Including HIPAA Authorization language as part of boilerplate language is permitted. The CIRB does not approve the HIPAA Authorization language as it does not function as a Privacy Board however the CIRB will accept HIPAA Authorization language when submitted as part of the boilerplate.

b) make no language changes to the consent form with the exception of NCI CIRB-approved boilerplate language;
c) obtain NCI CIRB approval of changes to the boilerplate language prior to implementation;
d) obtain NCI CIRB approval of translations of the consent form prior to implementation.

9) Maintain regulatory file for each study under NCI CIRB purview as per local institution and sponsor policy;

10) Conduct full board review of any study enrolling prisoners, since the NCI CIRB is not constituted to review studies enrolling prisoners.

Independent Review Process and Procedures
UMC investigators planning to conduct a study for which the NCI CIRB can serve as the IRB of record must first undergo local review to ensure compliance with institutional requirements that are not assessed by the CIRB's Local Context Subcommittee. The local review will be conducted by the UMC IRB Chair, Vice-Chair, or designee and IRB Coordinators on behalf of the institution.

UMC IRB will confirm that the 'Annual Principal Investigator Worksheet About Local Context' is approved by the NCI CIRB. The Signatory Institution Principal Investigator and/or research personnel must confirm that the study to be opened is on the CIRB menu. The UMC IRB Chair, Vice-Chair, or designee and the IRB Coordinators will conduct an administrative review of each study submission and decide on a study-by-study basis if the study may be opened through the NCI CIRB or to conduct its own local IRB full board review.

The following steps must be followed to prepare a submission for UMC IRB review:
NOTE: Do not submit a 'Study-Specific Worksheet About Local Context' to the CIRB prior to confirmation from the UMC IRB office that a study can be deferred to the NCI CIRB.

1) Obtain access to secured NCI CIRB sites

The UMC Principal Investigator for the study must have an NCI CIRB 'Annual Principal Investigator Worksheet About Local Context' on file with the CIRB prior to submitting a new study. To ensure that the information provided in the 'Annual Principal Investigator Worksheet About Local Context' is consistent with UMC policies and procedures, the UMC IRB will review the initial Worksheet for each Principal Investigator before it is submitted to the NCI CIRB.

In addition, the UMC IRB requires that all investigators sign and date the Investigator Declaration on the UMC IRB "Annual Principal Investigator Application for NCI CIRB Reviewed Human Research Protocols" annually to ensure that they will comply with the highest standards of ethical and professional conduct in accordance with federal, state and local regulations and institutional and UMC IRB policies governing the conduct of research involving human subjects. The UMC IRB Coordinator will ensure that there is an "Annual Principal Investigator Application for NCI CIRB Reviewed Human Research Protocols" on file.

The Principal Investigator and/or research personnel is responsible for preparing submission for the NCI CIRB and must have access to the CIRB Website Participant's Area and to the CIRB's IRB Manager. Only registered users of the NCI CIRB may access study documentation, receive communications from the CIRB, and maintain current study records.

2) Prepare and submit the following documents for a New Study to the UMC IRB for local review:

- Cooperative Group Study Protocol

- CIRB Final approval letter
- CTSU IRB Authorization form
- Draft copy of the 'Study-Specific Worksheet About Local Context'
- CIRB-approved Informed Consent Form, and Assent Form (if applicable) containing CIRB-approved UMC IRB boilerplate language and attached HIPAA Research Authorization Form (if applicable)
- List of all investigator and research personnel including:
    - Curriculum vitae
    - CITI education course certificate, equivalent human subjects training certificate or documented research experience on their Curriculum vitae
    - UMC Medical Staff Conflict of Interest disclosure statement (PI & Co-Investigators only)

3) Receive correspondence/acknowledgement from the UMC IRB

The submitted items will be reviewed by the UMC IRB Chair, Vice-Chair or designee along with the UMC IRB Coordinators on behalf of the institution to ensure that institutional requirements are met, such as training and absence of conflict of interest issues, consent forms and assent forms, if applicable, use the current CIRB -approved template and include all required UMC IRB boilerplate language, and HIPAA authorization forms (if applicable) meet UMC requirements. If revisions are needed, these will be communicated to the study team by the IRB coordinator. After any needed revisions have been resolved, the UMC IRB will issue an acknowledgement letter to the Signatory Institution Principal Investigator deferring/ceding oversight to the NCI CIRB.

Note: UMC has the responsibility to decide on a study-by-study basis whether to conduct its own local IRB full board review. Although this is a rare decision, the study teams will receive notification of this decision.

4) Study Closure or Terminations will be reported to the UMC IRB

Once the CIRB has reviewed and approved the study for conduct at UMC, the NCI CIRB is the IRB of record and is responsible for local site issues as well as study-wide oversight including continuations, and amendments.

13. CONTINUING REVIEW

Scheduled Review
Research approved by the UMC IRB is subject to continuing IRB review at least yearly, or more frequently at the discretion of the IRB in accordance with 45 CFR 46.109(e), except as described in 45 CFR 46.109(f). This review must take place before the approval expiration date; any lapse in approval will result in permanent closure of the study at UMC.

The timetable of continued review will be determined at the time of project approval upon consideration of appropriate factors including, but not limited to, the following:

- The number of proposed subjects;
- The expected term of the entire research or investigation;
- The risks to the subject.

The approval date and the expiration date are clearly noted on all IRB certifications sent to the PI and must be strictly adhered to. The expiration date is the last date that the protocol is approved. The calculation of the expiration date is one year from approval or as determined by the IRB board. As a courtesy, the IRB Coordinator will send a reminder of the

continuing review to the Principal Investigator and/or their research coordinator in advance of the protocol expiration date. It is the responsibility of the Principal Investigator to meet the deadline indicated on the Continuing Review Report and to fill out the UMC Continuing Review Form. By federal regulation, no extension to the expiration date can be granted. The report will include, but not be limited to:

- The full protocol, application, or a protocol summery containing the relevant information to determine whether the proposed research fulfills the criteria for approval.
- If there are any changes in the conflict of interest status relating to the research;
- The number of subjects accrued;
- A description of any adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, reason for withdrawal and/or complaints about the research;
- Amendments or modifications
- A summary of any recent literature, new findings which may relate to the subjects' willingness to continue participation, or other relevant information, especially information about risks associated with the research;
- Current risk-potential benefit assessment based on study results
- The research results obtained thus far;
- If the study is closed to accrual;
- Number of patients currently being followed;
- If the study is permanently closed;
- A copy of the current Informed Consent document.
- Proposed consent documents
- Recruitment materials

At least one IRB member is provided and reviews the complete protocol including any protocol modifications previously approved by the IRB. A part of the review will ensure that the current consent document is complete and accurate; the IRB will also report any significant new findings that arise from the review process to research participants if they relate to a participant's willingness to continue research or investigation.

Any research or investigation which is terminated or completed before the scheduled review date will be reported and closed, by final report submitted by the investigator to the IRB, within three months after termination or completion.

Continuing Review Not Required

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances (45 CFR 46.109(f)(1)):

(i) Research eligible for expedited review in accordance with 45 CFR 46.110;

(ii) Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) 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:
(A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

For studies not requiring continuing review researchers are required to submit a study closure form to the UMC IRB when approved studies have been completed. This is required for administrative purposes for accurately tracking what research is active.

Non-Scheduled Review

At its discretion, the IRB has the authority to observe or have a third party observe the research or investigation and the Informed Consent process.

The IRB may, where appropriate, obtain the services of persons outside of the IRB other than the investigators to assist with the review of research or investigation including, but not limited to, review for purposes of determining whether any material changes have occurred since initial approval or prior reviews.

Failure to Submit a Continuing Review Report

If an investigator fails to submit a continuing review report within the regulatory reporting period, the protocol will be suspended or terminated at UMC for failure to submit a continuing review report within the time period stipulated (one year or less, as deemed appropriate). All research activities must stop. All interventions and interaction on current enrolled participants must cease, unless the IRB finds an over-riding safety concern or ethical issue such that it is in the best interests of the individual participants to continue participating. Enrollment of participants must also cease.

14. EXEMPT FROM IRB REVIEW

The IRB Chair, Vice-Chair or designated reviewer is responsible for determining whether human subject research is exempt from the requirements of the Common Rule as outlined in 45CFR46.104(d)(1-8). The following categories of human subjects research are exempt from this policy:

1. Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
    i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
3. i. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
        (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
        (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
        (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

    ii. For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions

offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

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

4. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
    i. The identifiable private information or identifiable biospecimens are publicly available;
    ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not reidentify subjects;
    iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
    iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*
5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.
    i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.
6. Taste and food quality evaluation and consumer acceptance studies:
    i. If wholesome foods without additives are consumed, or
    ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to

be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).
8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
    i. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
    ii. An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

45 CFR 46.104(b) Use of the exemption categories for research subject to the requirements of subparts B, C, and D: Application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

(1) Subpart B. Each of the exemptions at this section may be applied to research subject to subpart B if the conditions of the exemption are met.

(2) Subpart C. The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

(3) Subpart D. The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

The IRB Chair, Vice-Chair or designated reviewer is responsible for reviewing and determining whether the research is exempt from 45 CFR 46. As part of this review, the IRB Chair, Vice-Chair or designated reviewer will consider whether informed consent can be waived and whether there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of the data. If the IRB Chair, Vice-Chair or designated reviewer determines that the research is exempt from the requirements of 45 CFR 46, annual review will not be required unless changes are made to the research that exceed the parameters of the exemption and require subsequent IRB review. The IRB Chair, Vice-Chair or designated reviewer may request additional information from the requestor to make the determination. If the research does not meet the criteria for exemption, the protocol is reviewed through the expedited review procedure or by full board review at a convened meeting of the IRB, as appropriate to the research activities.

Investigators are notified in writing that the research is exempt from further IRB review and that they may not make changes to the research activity without first discussing the changes with the IRB to determine whether the changes are within the parameters for exemption. If the research no longer meets the criteria for exemption, the investigator must resubmit the research for review by the IRB at a convened meeting or through the expedited review procedure.

The Department of Health and Human Services (DHHS) and FDA regulations apply to research involving human subjects, but there are some categories of research that the regulations state are considered exempt research. The research that falls into these special categories is subject to the institutional policies of the University Medical Center of Southern Nevada (UMC). To qualify as an exempt study, the research must fall within one of the specific regulatory categories AND satisfy the UMC institutional requirements.

In accordance with the provisions of 45 CFR 46.104 and 21 CFR 56.104, some human subject research may be exempt from the application of applicable regulations. However, these provisions do not allow for the Principal Investigator to determine the exempt status of his or her research; **the UMC IRB REQUIRES THAT ALL RESEARCH INVOLVING HUMAN SUBJECTS MUST BE SUBMITTED FOR REVIEW, REGARDLESS OF THE POSSIBILITY OF EXEMPTION.**

The UMC IRB will determine if a project is exempt, NOT the principal investigator. Any study that the UMC IRB believes is not exempt must receive either expedited or convened review by the UMC IRB.

Does the FDA provide any exemptions to IRB review?

- The FDA provides only three types of exemption:
  (1) Research which started before July 27, 1981, and either did not require FDA approval before that date, or, was subject to requirements for IRB review prior to that date, and remains subject to review by an IRB which meets FDA requirements;
- Emergency use of a test article, provided any such use is reported to the UMC IRB within 5 working days AND any future use of the test article at UMC is subjected to UMC IRB review;
- The taste and food quality evaluation provided for above in category (6).

Any other research subject to FDA regulation cannot be exempt. Research is subject to FDA regulation if it involves a drug, medical device, food, or other product regulated by the FDA.

Please use the Office of Human Research Protections (OHRP): Human Subject Regulations Decision Charts in Article XIII of this document to help determine if your research project meets criteria for exemption from IRB review.

15. COOPERATIVE APPROVAL

Cooperative approval will be available in those situations when a patient on an approved study at another institution requires hospitalization at University Medical Center.

Before contacting the IRB for authorization, the admitting physician will personally consult with the principal investigator to determine the need for the patient to remain in the study. If need is shown, the admitting physician will request that the approved protocol and informed consent be Faxed to the hospital pharmacy before the medication is brought into the hospital. All of the above documentation will be provided to the IRB at the time of the request.

16. SUBJECT RECRUITMENT

For research to be approved, the IRB must make the determination that selection of participants will be equitable. Prospective research should include the following in their application:

- Purpose of the Research;
- Setting in which the research will be conducted;

- Whether prospective participants will include vulnerable populations
- The selection (inclusion/exclusion) criteria
- Subject recruitment and enrollment procedures
- The amount and timing of payments to participants
- The possible influence that could occur if payment is given to participants

Recruitment of research subjects is the responsibility of the investigator. The investigator is responsible for recruiting subjects in a manner that is fair, ethical and equitable. All recruitment procedures and materials must be IRB approved. This includes: information contained in the advertisements, mode of communication, final copy of printed ads, and final audio/video taped advertisements.

Recruitment materials must be consistent with the approved IRB protocol, accurate and not coercive. The IRB will review advertising to ensure that the advertisements:

- Do not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and protocols;
- Do not include exculpatory language;
- Do not emphasize the payment of the amount to be paid, by such means as larger or bold type;
- Do not promise "free treatment" when the intent is only to say participants will not be charged for taking part in the investigation;
- Are limited to the information prospective participants need to determine their eligibility and interest such as:
    - The name and address of the investigator or research facility;
    - The purpose of the research or the condition under study
    - In summary form, the criteria that will be used to determine eligibility for the study;
    - A brief list of participation benefits, if any,
    - The time or other commitment required of the participants
    - The location of the research and the person or office to contact for further information.
- Do not make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with labeling by the FDA or other regulatory body.
- Do not use terms, such as "new treatment", "new medication", or "new drug" without explaining that the test article is investigational.

    Do not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

17. PAYMENT TO SUBJECTS

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other expenses incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid coercion of subjects. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

The IRB will review payments to subjects to determine that:

- The amount of payment and the proposed method and timing of disbursement is neither coercive nor presents undue influence
- Credit for payment accrues as the study progresses and is not contingent upon the subject completing the entire study
- Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn;

- All information concerning payment, including the amount and schedule of payments, is set forth in the consent document.

Payments to research subjects and schedule of all payments must be disclosed in the informed consent document and documented in the IRB application.

18. VULNERABLE POPULATIONS

Research involving: Pregnant Women, Fetuses, and Neonates

The following guidelines apply to all biomedical and behavioral research conducted at UMC or its affiliated organizations involving pregnant women, human fetuses, neonates as subjects. The requirements concerning review of research that involves pregnant women, human fetuses, and neonates are transcribed below. This group could be potentially vulnerable to coercion in regard to autonomy, and present conditions that may affect risk/benefit determinations or bearing unequal burden in research.

As noted above, the following policies only apply to biomedical research and non-biomedical research which might affect the health and welfare of human fetuses or neonates. These policies are based on 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.
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 delivery.
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.
Neonate:	A newborn.
Nonviable neonate:	A neonate after delivery that, although living, is not viable.
Pregnancy:	The period of time from implantation until delivery. A woman is 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 Neonate:	A neonate after delivery that, is able to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Research Involving Pregnant Women or Fetuses [45 CFR 46.204]

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

1) Where scientifically appropriate, pre-clinical 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;
2) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, there is minimal risk for the fetus and the

purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

3) Any risk is the least possible for achieving the objectives of the research;
4) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal risk and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the provisions for informed consent;
5) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6) Each individual providing consent under paragraph 4) or 5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7) For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent;
8) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9) 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
10) Individuals engaged in the research will have no part in determining the viability of a neonate.

Research Involving Neonates [45 CFR 46.205]
Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2) Each individual providing consent 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 Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) 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:

The IRB determines that:

- The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
- 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
- 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 the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.
- Individuals giving legally effective informed consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate.

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:

- Vital functions of the neonate will not be artificially maintained;
- The research will not terminate the heartbeat or respiration of the neonate;
- There will be no added risk to the neonate resulting from the research;
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.
- However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

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 accordance with the requirements of initial review and research involving children

Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material [45 CFR 46.206]128]

1) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must 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 above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of this policy are applicable.

Research Not Otherwise Approvable [45 CFR 46.207]
The Secretary of the Department of Health and Human Services (HHS) will fund research that the IRB does not believe meets the requirements of **Research Involving Pregnant Women or Fetuses or Research Involving Neonates** only if:

1) 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
2) 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:
    a. That the research in fact satisfies the conditions of Research Involving Pregnant Women or Fetuses, as applicable; or
    b. The following:
        i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
        ii. The research will be conducted in accordance with sound ethical principles; and
        iii. Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this policy.

IRB Review
The IRB members will determine the risk and benefit assessments, and the requirements for consent, permission, and/or assent by parents/guardians and children.

Inclusion of Women and Minorities in Research
The IRB will review protocols to ensure that an equitable selection of research participants is evident. Investigators will provide details of the proposed involvement of humans in the research including the characteristics of the subject population, anticipated numbers, age ranges, and health status. Other characteristics to be identified include gender and racial/ethnic composition and inclusion or exclusion of any sub-population.

Research involving: Prisoners
The following guidelines apply to all biomedical and behavioral research conducted at UMC or its affiliated organizations involving prisoners as subjects. Even though a UMC IRB may approve a research protocol involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the Nevada Department of Corrections and any other applicable State or local law. [45 CFR 46.301] Research involving prisoners requires certification by the Department of Health and Human Services (HHS) for research conducted or funded by federal HHS.

Because prisoners may be under constraints because of their incarceration, which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is important to provide additional safeguards for the protection of prisoners involved in research activities to which this subpart is applicable. [45 CFR 46.302]

These policies apply to all research involving prisoners and are based on 45 CFR 46, Subpart C.

Definitions **[According to 45 CFR 46.303]**

Prisoner:	An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)]
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

Composition of the IRB [45 CFR 46.304]
In addition to satisfying the general requirements detailed in the IRB section of this policy, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB.
2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB. The prison representative will serve as an ad hoc voting member of the IRB on research regarding prisoners.

Additional Duties of the IRB [45 CFR 46.305]
In addition to all other responsibilities prescribed for the UMC IRB in the UMC Institutional Review Board policies, the IRB will review research involving prisoners and approve such research only if it finds that:

1) the research falls into one of the following **permitted categories** [45 CFR 46.306]:
   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 no more than inconvenience to the subjects;
   b) study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
   c) research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
   d) research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
3) the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers, and that the risks that face prisoners in the prison setting is not used as the standard for acceptable risk;
4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the 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;
5) the information is presented in language which is understandable to the subject population;
6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
7) where the IRB finds there may be a need for follow-up examination or care of subjects 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 subjects of this fact.

Waiver for Epidemiology Research
The Secretary of HHS has waived the applicability of 45 CFR 46.305(a)(l) and 46.306(a)(2) for certain research conducted or supported by federal HHS that involves epidemiologic studies that meet the following criteria:

1. In which the sole purposes are:
    a. To describe the prevalence or incidence of a disease by identifying all cases, or
    b. To study potential risk factor associations for a disease, and
2. Where the IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) [see 2) – 7) above] and determined and documented that:
    a. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
    b. Prisoners are not a particular focus of the research.

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject subjects. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.

In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.132

Research involving: Children
The following guidelines apply to all biomedical and behavioral research conducted at UMC or its affiliated organizations involving children as subjects. The ethical mandate of IRB is to protect the rights and welfare of human research subjects. IRB's are obligated to ensure that research studies do not endanger the safety or well-being, of human subjects or undermine public confidence in the conduct of research. The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children.

Federal regulations (45 CFR 46 Subpart D) provide additional protection for children involved in research, such as obtaining assent of the children and the permission of the parents/guardians. More specific provisions are based on the

degree of risk involved in the proposed research, and the nature and degree of anticipated benefit(s). These are described below.

Exemptions applicable to research in adults (45 CFR 46.101 and section of this manual) also apply to children, except that the exemption for research involving survey or interview procedures or observations of public behavior does not apply unless the investigator(s) does not participate in the activities being observed (45 CFR 46.401).

Definitions

Assent:	A child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent [45 CFR 46.402(b)].
Benefit:	A valued or desired outcome; an advantage.
Children:	Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted (45 CFR 46.402(a)].
Emancipated Minor:	A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation. *(See also: Mature Minor.)*
Guardian:	An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402(3)].
Mature Minor:	Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor. *(See also: Emancipated Minor.)*
Minimal Risk:	A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during, the performance of routine physical or psychological examinations or tests [Federal Policy §_. 102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.
Parent:	A child’s biological or adoptive parent
Permission:	The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].
Risk:	The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only of minimal risk" *(See also: Minimal Risk.).*

Emancipated Minor: A minor is considered emancipated under the following circumstances:

Without a court order:

- when a minor is married;
- when he/she has reached the age of 18 years;

- when a minor is on duty with -the US armed forces;
- for purposes of consenting to routine non-surgical medical care or emergency medical treatment when a minor is in the custody of a law enforcement agency and the minor's parents or guardian cannot be located;
- for purposes of consenting to his or her own preventative health care medical care including surgery, dental care, or mental health care, except vasectomies or any procedure related to reproduction, during the period when the minor is a prisoner under the department of corrections or the period when the minor is a probationer residing in a
- special alternative incarceration act, but only if the parent or guardian cannot be located by the department of corrections.

By Court Order: The court will issue an emancipation order if it determines that emancipation is in the best interest of the minor and the minor is able to establish one of the following.

- the minor's parent or guardian does not object to the emancipation or if the parent or guardian does object, the parent or guardian is not supporting the minor,
- the minor is at least 16 years of age;
- the minor is a Nevadan resident;
- the minor has demonstrated the ability to manage his or her financial affairs, including proof of employment or other means of support;
- the minor has the ability to manage his or her personal and social affairs, including but not limited to housing; and
- the minor understands his or her rights under the act as an emancipated minor

Analysis of Probable Risks, Possible Benefits, & Associated Discomforts

IRB's reviewing research involving children as subjects must consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. In calculating the degree of risk and benefit, the IRB should weigh the circumstances of the subjects under study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

The federal regulations require IRB's to classify research involving children into one of four categories and to document their discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by IRBS, based on degree of risk and benefit to individual subjects, are as follows:

1) §46.404 - RESEARCH NOT INVOLVING GREATER THAN MINIMAL RISK- may be done provided that parents/guardians give permission and the child gives assent, as appropriate, to participate in research.

2) §46.405 - RESEARCH INVOLVING GREATER THAN MINIMAL RISK BUT PRESENTING THE PROSPECT OF DIRECT BENEFIT TO THE INDIVIDUAL SUBJECTS - may be done if:
   - The risk is justified by the anticipated benefit to subjects;
     OR
   - The relationship of the benefits to the risk is at least as favorable to the subject as that presented by available and alternative approaches;
     AND
   - The parents/guardian will give permission and child *will give* assent as appropriate to participate in research.

3) §46.406 - RESEARCH INVOLVING GREATER THAN MINIMAL RISK AND NO PROSPECT OF DIRECT BENEFIT TO THE INDIVIDUAL SUBJECTS, BUT LIKELY TO YIELD GENERALIZABLE KNOWLEDGE ABOUT THE SUBJECTS DISORDER OR CONDITION-Such research will be considered on a case-by-case basis and must meet the following standards:
    - The additional risk represents only a minor increase over minimal risk;
    - The intervention or procedure presents experience to the children that are reasonably commensurate with those inherent in their actual or expected medical condition;
    - The intervention or procedure is likely to yield generalized knowledge about the subject's disorder or condition that is of vital importance for the understanding or treatment of the disorder or condition in children.
    - The parents/guardian give permission and the child gives assent, as appropriate, to participate in the research. It is advisable that the Principal Investigator considers including a disinterested party as the person who informs the subject and/or family and obtains the consent.

    Please note that written assent is recommended for children over the age of 13 years and oral assent is recommended for children over the age of 8 years for all three categories of risk.

4) §46.407 - RESEARCH NOT OTHERWISE APPROVABLE, BUT WHICH PRESENTS AN OPPORTUNITY TO UNDERSTAND, PREVENT, OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELFARE OF CHILDREN - Research that is not approvable under 45 CFR 46.404, 46.405, or 46.406 may be conducted or funded by DHHS provided that the IRB, and the Secretary, after consultation with a panel of experts, finds that the research presents a reasonable opportunity to further the understanding,, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles [45 CFR 46.407].

In all cases, the IRB must determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians (45 CFR 46.408].

Assessing Probable Risks:

Central to IRB's' consideration of research involving children is the determination of what constitutes minimal risk. Procedures that usually present no more than minimal risk to a healthy child include: urinalyses, obtaining small blood samples, EEGS, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. The assessment of the probability and magnitude of the risk, however, may be different in sick children and may vary depending on the diseases or conditions the subjects may have. For example, obtaining blood samples from a hemophiliac child may present more than minimal risk to the child. On the other hand, IRB's may consider that children suffering from chronic illnesses who are accustomed to invasive procedures are placed at minimal risk by involvement in similar research procedures, in contrast to children who have not had such experiences. The IRB must also consider the extent to which research procedures would be a burden to any child, regardless of whether the child is accustomed to the proposed procedures.

Procedures that exceed the limits of minimal risk may be difficult to define in the abstract, but should not be too difficult to identify on a case-by-case basis. Riskier procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress may also exceed minimal risk.

Assessing Possible Benefits:

In assessing the possible benefits of research intervention, the IRB should consider the variability in health statuses among potential subjects. For example, a potential subject might be a normal, healthy child, or a child who has been exposed to a disease or a toxin (e.g., meningococus or lead) where it is known that a percentage of the children exposed will actually experience untoward consequences. A child may also be in an early state of disease, e.g., an HIV-infected child, or may

actually suffer from disease or other significant medical condition. Thus the IRB must take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

Phase I Trials, some diseases specific to children may require that children be involved without data from older groups (e.g., there is no adult model that mimics the state of HIV-infected newborns; Wilms' tumor and various cancers such as neuroblastoma affect infants who do not survive into older childhood.) In some cases, "tandem" studies in older populations and children may be justifiable. For example, some Phase 1 studies in children might be based on only pharmacologic safety and toxicity data (completed Phase 1 and ongoing Phase 2) but without complete effectiveness data from trials in adults and older children. If the IRB approves a Phase 1 drug trial, the consent document must specify what is known about the probability that, and the degree to which, an intervention will be of possible benefit based on all of these data.

Recruitment of Children Who Are Not Patients
Children age 13 years and over may be recruited for certain *minimal risk research* at the discretion of the IRB, by posted notices, public or printed announcements, or by letter. The kind of research that might qualify includes observational studies, educational tests, and questionnaires with non-sensitive content.

Children under the age of 13 may be recruited for *minimal risk research* only through written announcements to, or direct contact with, the parents/guardians describing the research, including general procedures and time periods, and any expected discomforts and major, risks as well as expected benefits.

For more than minimal risk or research all subjects may be recruited only through written announcements to, or direct contact with, the parents/guardians describing the research, including general procedures and time periods, and any expected discomforts and major risks as well as expected benefits.

Other Considerations
The wordings of the consent form for a given Protocol should include the combinations 'I/my child', “my/my child's", etc.- as appropriate to the context and syntax.

Consent Procedures
When children or minors are involved in research, the regulations require the **assent** of the child or minor and the **permission** of the parent(s), or legally authorized representatives, in place of the consent of the subjects.

The IRB must determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered "not reasonably available" [45 CFR 46.408]. (Examples of circumstances in which parental permission may be inappropriate are discussed below.) In addition, the regulations require that the IRB determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent [45 CFR 46.408(a)]. When assent is a requirement, assent will be documented and acquired in compliance with regulations and UMC informed consent policies.

1) *Permission of PARENTS-* The regulations provide that an IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 (minimal risk research) or 45 CFR 46.405 (research involving, greater than minimal risk but presenting the prospect of direct benefit to individual subjects) [45 CFR 46.408(b)].

   Where research is covered by 45 CFR 46.406 (greater than minimal risk with no direct benefit) and 45 CFR 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 [45 CFR 46.408(b)).

2) *Assent of the CHILD-* While children may be legally incapable of giving, informed consent, they nevertheless may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. The IRB must determine for each protocol - depending on such factors as the nature of the research and the age, status, and condition of the proposed subjects - whether all or some of the children are capable of assenting to participation. Where appropriate, IRB's may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. The federal regulations do not require that assent be sought from children beyond a specific age, but that their assent should be sought when, in the judgment of the IRB, the children are capable of providing their assent. IRB's are to take into account the ages, maturity, and psychological state of the children involved [45 CFR 46.408(a)].

3) *Assent of Child UNNECESSARY-* When the research offers the child the possibility of a direct benefit that is important to the health or wellbeing of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary [45 CFR 46.408(a)]. Additionally, in such circumstances a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening, diseases such as cancer, however, IRB's should be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

4) *Parental Permission UNNECESSARY*-The requirement for parental permission may be inappropriate in some cases. Examples include research involving older adolescents who, under applicable law, may consent on their own behalf for selected treatments (e.g., treatment for venereal disease, drug abuse, or emotional disorders). In other research (e.g., research on child abuse or neglect), there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these cases, IRB's should devise alternative procedures for protecting the rights and interests of the children asked to participate, including, perhaps, the court appointment of special guardians.

5) *Parental Permission INSUFFICIENT*-Parental permission may sometimes be insufficient to protect the child's interests. In cases involving transplants (e.g., of bone marrow or a kidney) between minor siblings, the parents' concern for the afflicted child may interfere with their consideration of the best interests of the healthy donor. Therefore, IRB's may want to consider asking for court review of the parents' decision. *[See also* Guidebook Chapter 5, Section G, "Transplants."]

6) *Applicability of STATE LAWS*-The IRB should consult legal counsel about the applicability of any state laws affecting consent for the proposed research. The IRB should be aware of the age of majority in the state as well as laws or court decisions that might limit the right of parents to consent on behalf of their children in certain circumstances. Ace and conditions of emancipation will differ from state to state. In some states the age at which a child can give consent to medical care differs depending on the medical condition involved (e.g., venereal diseases). The federal regulations require that all research activities must comply not only with the regulations but also with the law of the state in which they are performed.

7) *Adequacy of the Provisions for Obtaining and Documenting Assent* [45 CFR 46.408(e)] - *The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she *ag*rees to participate.

**For some research activities, IRB's may require that either an IRB member or an advocate for the child be*

*present during the assent and permission procedures to verify the child's understanding and to support the child's preferences. The IRB may also require that the parent(s) or a close family member be present during the research, especially if a young child will be exposed to significant discomfort or inconvenience, or if the child will be required **to** spend time in an unfamiliar place.*

Exemption from Review

The exemption at 45 CFR 46.104(b)(3), allow for exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D; as stated in Section 14 of this policy.

Wards of the State

The special protections for children set forth in Subpart **D** include additional limitations on some research involving children who are wards of the state or any other agency, institution, or entity. Where the research involves greater than minimal risk to the subjects with no prospect of direct benefit to individual subjects (45 CFR 46.406), or requires HHS Secretarial approval (45 CFR 46.407), the research must either be related to their status as wards, or else be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards [45 CFR 46.409]. The IRB must require, for each child who is a ward, appointment of an advocate in addition **to** any other individual acting on behalf of the child as a guardian or *in loco parentis.*

IRB's should be particularly concerned with the involvement of HIV-infected children **who** are in foster care, but who are also not wards. Many of these children are from racial **or** ethnic minorities. IRB's need to give special attention to groups of children such as these who, while they need special protections, should not be denied the opportunity to participate in research that may potentially be of benefit to them.

Finally, whenever institutionalized children might be involved in research, care should be taken to ensure that they are not included as participants simply because of their availability to the investigator.

Points to Consider

1) Does the research have an identifiable prospect of direct benefit to the individual child participant? Can that benefit be achieved through alternative means?
2) Does the research have an identifiable prospect of risk to the individual child participant? What safeguards are proposed to minimize these risks? When procedures involving greater than minimal risk to children are anticipated, are convincing scientific and ethical justifications given?
3) Is the inclusion of normal volunteers justified?
4) Do studies involving placebo controls place the child at greater risk by withholding from selected subjects potentially therapeutic research drugs or interventions?
5) When possible, have appropriate studies been conducted on animals and adults first? Will older children be enrolled before younger ones?
6) What is the age of majority in the state? Can a child consent to medical care for certain conditions, and, if so, at what age? What legal limits are there on the right of parents to consent on behalf of their children?
7) Is permission of both parents necessary? Under what conditions may one of the parents be considered "not reasonably available?"
8) Will efforts be made to ensure that parents' permission to involve their children in research studies is free from coercion, exploitation, and/or unrealistic promises?
9) Are mechanisms in place to ensure that children are involved as research subjects in ways that do not undermine their dignity as young persons? Are provisions made that show respect for the developing rights of children, such as: (a) obtaining their assent, and, where appropriate, honoring, their dissent; and (b) protecting their need for privacy and the confidentiality of information regarding them?
10) Are there special problems that call for the presence of a monitor or advocate during consent procedures?

11) Are special needs of adolescents such as counseling and confidentiality accounted for in the research design?
12) Are there any special problems such as confidentiality and reporting that might arise in sensitive research about child abuse or sexual practices of teenagers?
13) If conditions present in children have implications for other family members' health statuses, are appropriate mechanisms proposed for dealing with the larger family unit (e.g., genetic risks or HIV infection)? Should parents be required to be present during the conduct of the research? (Are proposed subjects to be very young? Are the procedures involved painful? Must subjects stay overnight in the hospital when they otherwise would not have to?

Research involving: Persons with mental disabilities or persons with impaired decision-making capacity The following guidelines applies to all biomedical and behavioral research conducted at UMC or its affiliated organizations involving subjects who are mentally ill or subjects with impaired decision-making capacity. This vulnerable population warrants special attention. Research involving these populations may present greater than minimal risk; may not offer direct medical benefit to the subject; and may include a research design that calls for washout, placebo, or symptom provocation. In addition, these populations are considered to be vulnerable to coercion.

IRB Composition
The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.

Approval Criteria
Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

- Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
- The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
- Procedures have been devised to ensure that subject's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents [appointed under Durable Power of Attorney for Health Care (DPAHC)] and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

The IRB members will determine the risk and benefit assessments, and the requirements for surrogate consent in accordance with general requirements of informed consent.

Additional Concerns
Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. It is the responsibility of investigators to monitor the decision-making capacity of subjects enrolled in research studies and to determine if surrogate consent must be re-obtained. The IRB will evaluate whether the proposed plan for the assessment of the capacity to consent is adequate and if assent of the participant is a requirement.

The IRB will require investigators to conduct a competency assessment whenever there is a possibility of either impaired mental status or decision-making capacity in prospective subjects.
Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

Vulnerable Subjects requiring further IRB review
These guidelines describe the review of specific types of research that require additional considerations by the IRB. The activities described below involve either research or methodology that might require additional consideration that the IRBs are required to make and document. These types of research include, but are not limited to:

a) Nevada System of Higher Education (NSHE) Students and Employees as Subjects
b) Normal Volunteers
c) Terminally Ill patients
d) Genetic research
e) Research Involving Coded Private Information or Biological Specimens

NSHE Students and Employees as Subjects
When NSHE students and/or employees are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. The voluntary nature of Investigators must emphasize to subjects that neither their academic status or grades, or their employment, will be affected by their participation decision.

To minimize coercion, investigators should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes other than their own. When entering a classroom to recruit students and conduct research, e.g. administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

Normal Volunteers
Normal Volunteers can be defined as a healthy person who volunteers to participate in research. Risks that these individuals, with whom there is no direct therapeutic benefit, should be minimized to the greatest extent possible. While minimization of risks is important for any research conducted, the altruistic motivations of these volunteers (i.e. contributing to scientific knowledge for the benefit of society) emphasis the ethical concern for the risks that these individuals face. The IRB should scrutinize the compensation that is offered to these volunteers. The monetary compensation should not be so great as to induce assent.

Terminally Ill patients
Terminally ill patients are defined as persons deteriorating from a life-threatening disease or condition for which no effective standard treatment exists. Terminally ill patients should not be excluded from research in which they want to participate because of their status as a terminally ill patient. However, precautions must be taken to ensure that they are autonomous in their decision and that there is no coercion or undue influence. [45 CFR 46.111(b)]. Consultation with family members, friends, clergy, or medical consultants should be encouraged and relevant information should be provided to the patient to make an informed decision.

Genetic Research
Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed, including:

- Will test results be given?
- Will disease risk be quantified, including the limits on certainty of the testing?
- Will a change in a family relationship be disclosed, such as mistaken paternity?
- Does the subject or family member have the option not to know the results? How will this decision be recorded?
- Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
- Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
- Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

- Will DNA be stored or shared? If shared, will the subject's identity be known by the new recipient investigator?
- Will the subject be contacted in the future by the investigator to obtain updated clinical information?
- How can the subject opt out of any distribution or subsequent use of his/her genetic material?

Research Involving Coded Private Information or Biological Specimens

UMC policy is based on the OHRP guidance document entitled, *Guidance on Research Involving Coded Private Information or Biological Specimens* (August 10, 2004 http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf). This document:

- Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under federal HHS regulations for the protection of human research subjects (45 CFR 46).
- Reaffirms OHRP policy that, under certain limited conditions, research involving only coded private information or specimens is not human subject research.
- Provides guidance on who should determine whether human subjects are involved in research

For purposes of this policy, *coded* means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Under the definition of human subject, obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining means receiving or accessing identifiable private information or identifiable specimens for research purposes. This includes an investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do **not** involve human subjects if the following conditions are both met:

- the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
    - the key to decipher the code is destroyed before the research begins;

- the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the federal HHS regulations do not require the IRB to review and approve this agreement);
- there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
- there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases, an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subject research is determined to be exempt, IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent.

Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research
The investigator in consultation with the IRB Chair, Director of the UMC IRB, or IRB staff will determine if the research involving coded information or specimens requires IRB review. If the request is verbal (by phone or in person) or by email, it is the investigator's responsibility to maintain documentation of such a decision. If the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

19. EMANCIPATED MINOR

(Refer to UMC Administrative Policy & Procedure Manual, Policy #1-3.1)

20. INFORMED CONSENT

Except as provided in Section 56.109 (c), informed consent will be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy will be given to the person signing the form. The investigator will be responsible for placing a signed copy of the approved consent form into the medical record of subjects admitted to the hospital.

Requirements for Obtaining Informed Consent
Unless otherwise authorized by the IRB, research investigators are responsible for ensuring that the Informed Consent will:

- Be obtained from the subject or the subject's legally authorized representative;
- Be in a language and vocabulary understandable to the subject or representative;
- Be obtained under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate, and an opportunity to discuss;
- Not include statements that waive, or appear to waive, any of the subject's legal rights or release the institution, its agents, the sponsor, or the investigator from liability for negligence.
- Except for broad consent must contain concise and focused key information and must be organized and presented in a way to facilitate understanding of one's reason to want to participate
- Be in circumstances of the consent process minimize the possibility of coercion or undue influence.
- Embody the basic and required additional elements of disclosure
- The informed consent requirements are not intended to preempt any applicable federal, state or local laws, which require additional information to be disclosed for informed consent to be legally effective.

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

The IRB may allow a waiver or alter of the consent process by determining that the criteria for waivers of alterations of the consent process are met. Documentation of the consent process may be waived if the IRB determines that the research presents no more than minimal risk of harm to participants and that the research involves no procedures for which written documentation of the consent process is normally required outside of the research context. When the IRB considers waiving the requirement to obtain written documentation of the consent process, the IRB reviews a written description of the information to be provided to participants. The consent process and parental permission cannot be waived or altered for FDA regulated research.

Elements of Informed Consent
In seeking informed consent, the following elements of informed consent will be provided to each subject, in lay terms/vocabulary:

Required Elements:
Unless informed consent is waived or altered by the IRB, the consent process must include the following basic elements:

- A statement that the study involves research, explanation of the purposes of the research, expected duration of the subject's participation, description of the procedures to be followed, and identification or any procedures that are experimental.
- Description of any reasonably foreseeable risks or discomforts to the participant.
- Description of any benefits to the participant or to others that may reasonably be expected from the research
- Disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the participant
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, in compliance with HIPAA regulations, and that notes the possibility that the USFDA may inspect the records. To insure that patients are fully informed regarding the disclosure of their protected health information, the IRB prefers that the "UMC Authorization to Use and Disclose PHI for Research Purposes" be completed. However, if these elements are contained within the consent, the IRB will make exceptions on a case-by-case basis.
- Explanation of whom to contact for answers to pertinent questions about the research and research participant's rights and whom to contact in the event of a research-related injury to the participant.
- Statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled
- Contact information for the research team for questions, concerns, or complaints.
- Contact information for someone independent of the research team for problems, concerns, questions, information, input (List the UMC IRB office).
- If the research involves the collection of identifiable private information or identifiable biospecimens one of the following statements:
    - identifiers might 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; or
    - 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
- If the study involves more that minimal risk:
    - An explanation as to whether compensation is available if injury occurs
    - If compensation is available when injury occurs, an explanation as to what it consists of or where further information can be obtained;
    - An explanation as to whether any medical treatments are available if injury occurs.

- If medical treatments are billable when injury occurs, an explanation as to what it consists of or where further information can be obtained.

- For research regulated by the FDA, a statement that informs the participant of the possibility that FDA may inspect the records.
- The research has received IRB Approval.
- To comply with the Federal Health Insurance Portability and Accountability Act (HIPAA), the following statement must be included:
  - UMC has rules to protect information about you. Federal and state laws also protect your privacy. Protected Health Information (PHI) is any health information that identifies you. Generally, only people on the research team will know that you are in the research study and will see your information. Unless you give permission or the board that reviews research studies approves it, no one else will be able to see or use your information.
  - The people working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes other people at UMC may see or give out your information. These include people who review the research studies, their staff, lawyers or other UMC staff.
  - People outside of UMC may need to see your information for this study. Examples include government groups, safety monitors, and other hospitals in the study and companies that sponsor the study. For any research that is subject to audit or inspection by any funding agency or sponsor, include a statement indicating that the sponsor may choose to inspect and copy medical or research records that identify individual research subjects.
  - You will be asked to authorize the use and disclosure of your protected health information on a separate document. We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.
  - In the event of any publication regarding this study, your identity will not be disclosed. (Use the ***UMC Authorization to Use and Disclose Protected Health Information for Research Purposes*** Form).
- To comply with 21 CFR § 50.25(c), applicable clinical trials that must report to www.ClinicalTrials.gov must include the statement below:
  - "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."
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Additional Elements

The following requirements should be provided to potential participants during the consent process, when appropriate:

- Statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) that are currently unforeseeable
- Anticipated circumstances under which participation may be terminated by the investigator without regard to the participant's consent
- Any additional costs to the participant that may result from participating in the research
- Consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant
- Statement that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided
- Approximate number of participants involved in the study
- 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

- statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
- In the use of an investigational device, an explanation of the expected duration and purpose of the use of the investigational device is to be given.
    - Whether or not there is need for hospitalization;
    - A statement that the participant will be notified of significant new findings developed during the course of the research.

Elements of Broad Consent

Elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens. Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes) is permitted as an alternative to the informed consent requirements in paragraphs (b) and (c) of this section. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

- A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
- A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
- A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
- Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;
- Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and
- An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

The IRB may require additional information beyond the basic and additional elements of consent when the information would meaningfully add to the protection of research participants. Examples of this include:

- A statement that the particular treatment or procedure may involve risks to the embryo or fetus, if the subject is female and is (or may) become pregnant, or if the subject is male, if he impregnates a spouse or significant other.
- An explanation of likely results should the treatment or procedure fail.
- A disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.

- A statement that the Principal Investigator and/or his/her institution will (or will not) receive any compensation for recruiting and enrolling patients in research protocols.
- Notice that no compensation or free medical care has been set aside by University Medical Center for patients enrolled in research studies.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- If the study involves use of an investigational device, a statement clarifying whether the device will be retrieved if death occurs; and, if autopsy is required, who is financially responsible.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- The approximate number of subjects involved in the study, both nationwide and locally.
- A statement acknowledging that the subject will receive a signed copy of the Informed Consent Form.

Process to gain consent

- The researcher will obtain the legally effective consent of the participant or the participants legally authorized representative.
- The circumstances of the consent process provide the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate.
- The circumstances of the consent process minimize the possibility of coercion or undue influence.
- The consent document embodies the basic and required additional elements of disclosure
- The participant or the participants legally authorized representative will sign and date the consent document;
- A copy of the signed and dated consent form will be given to the person signing the consent form;
- The researcher will give either the participant or the legally authorized representative adequate opportunity to read the consent document before it is signed.
- The individuals communicating information to the participant or the legally authorized representative during the consent process will provide the information in language understandable to the participant or the representative.
- The information being communicated to the participant or the representative during the consent process will not include exculpatory language through which the participant or the legally authorized representative is made to waive or appear to waive any of the participant's legal rights.
- The information being communicated to the participant or the legally authorized representative during the consent process will not include exculpatory language through which the participant or legally authorized representative releases or appears to release the researcher, the sponsor, the investigative site, or its agents from liability for negligence.

The IRB will evaluate whether research involves participants who have diminished decision making capacity and, if so, provide additional safeguards to ensure an appropriate consent process. When a research study involves populations with diminished decision-making capacity not covered by UMC policies, an IRB member will review research and precedent to evaluate the consent process for these populations.

Consent Observation

The IRB has the authority to observe or have a third party observe the informed consent process and/or audit the progress of any study in its jurisdiction as it deems necessary to protect the rights and welfare of human subjects.

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may require special monitoring of the consent process by an impartial observer (consent monitor) in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB Chair and the Director will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with the institution. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of subjects. Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

Re-Consenting

Under certain circumstances it may be necessary for subjects to re-consent to participate in a study. The IRB will consider the need to re-consent on a protocol-by-protocol basis or a case-by-case-basis.

The following are among the situations when the IRB may require a subject be re-consented:

- A minor was enrolled in a study and s/he attains age eighteen (18) years while still in the study. The subject would legally be an adult and his/her consent would be required to continue participation in the study, and as applicable, consent would be required for optional tissue banking and genetic testing.
    - *When minors may be enrolled in a study and could have specimens banked and genetic testing performed on them, the protocol is to include a plan to contact subjects enrolled as minors who attain age 18 years to inform them of the study. Such individuals might not be located; in such case, the Principal Investigator will be instructed to document that reasonable efforts to contact and inform the individual were made. The Principal Investigator should be advised that failure to obtain consent at age 18 years may hamper future research on banked samples, as at age 18 years subjects must consent to tissue banking and genetic testing or be able to withdraw their samples from being banked. The investigator should include an explanation for what will happen to banked specimens if the subject cannot be reached when the subject reaches the age of majority. It is the IRB's preference that in these instances, the existing tissue be fully de-identified.*
- An individual was temporarily incompetent when initially enrolled in a study, or was enrolled in a study conducted in an emergency setting.
- A subject participates in a longitudinal study. If the study is particularly long, re-consenting the subject may be necessary to maintain a subject's understanding of the relevant research activities. Investigators should present a plan for maintaining informed consent when submitting protocols where subjects will be followed over long periods of time.
- The research has changed, or important new information relevant to the subject's continued participation is discovered. Investigators should address whether re-consent is necessary at time of discovering new information, submission of AE's, or protocol amendment.

Informed Consent and Language Barriers

Researchers should prepare both English language and translated consent forms for proposals that include non-English speaking subjects. A "Certificate of Translation" shall be provided along with the translated consent form as evidence of the documents accuracy.

If a non-English-speaking subject is enrolled unexpectedly, researchers may rely on an oral translation of the English language consent form, but should take extra care in the informed consent process to ensure that the subject has understood the project. A statement in the research records (and on the English language consent form) should indicate that the translation took place, identify the translator, and document the translator's belief that the subject understands the study and the consent process. If the subject is a patient, a note about the translation should be made in the patient's research records as well. Researchers should try to provide a written translation of the vital emergency contact information.

Sometimes a subject understands English but does not read or write English. Again, an impartial witness should document that the subject understands the research and the consent process and consented to participate.

Research Data Retention

The following guidelines regarding research data retention applies to FDA – regulated research.

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remain part of the study database and may not be removed
- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant must distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and addresses the maintenance of confidentiality of the participant's information.
- If a participant withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information, the researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of the consent documents is required.
- If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participants consent. However, a researcher may review study data related to the participant collected prior to the participants' withdrawal from the study, and may consult public records, such as those establishing survival status.

Remote Consent

When the IRB approves a phone consent process that requires the subject's signature on the consent document, the following steps should be taken and documented in the IRB Submission Application (either New or Amended):

- The study team confirms the potential subject's interest in learning more about the study and verifies the mailing address or email address.
    - If the consent is an Electronic Consent, it must follow the FDA's requirements set forth in 21 CFR parts 11, 50, and 56, respectively. HHS requirements regarding the protection of human subjects are set forth in 45 CFR part 46.
    - If the consent form will be sent by postal mail, the blank consent form is mailed, along with a cover letter that introduces the study and explains when the phone conversation will occur. A stamped, self-addressed envelope is provided so the subject can return the signed consent document to the study team.
    - Alternatively, if the subject agrees to email communication, the consent form is sent by secure email.
- After the potential subject has received the document, a member of the study team calls the subject and walks through the entire document over the phone, answering questions and making notes about the subject's questions. Time and date of the conversation should be recorded.
- Once all questions are answered, the subject signs the consent form if they are willing to participate.
    - S/he returns the consent form by mail in the provided self-addressed envelope.
    - Alternatively, the consent form should be scanned by the subject and returned to the study team by email.
    - The subject signs the document electronically, using acceptable methods for research under FDA regulations and not under FDA regulations.
    - The subject signs the electronic consent. FDA's requirements for electronic records/electronic signatures, informed consent, and IRBs are set forth in 21 CFR parts 11, 50, and 56, respectively. HHS requirements regarding the protection of human subjects are set forth in 45 CFR part 46.
- Once the signed version is returned, the study team member who conducted the consent conversation should sign the consent form and date with the current date. If postal mail is used, explain the discrepancy in dates. The study

team member should write a note on the consent form stating that the subject's consent was obtained by phone on xx date (the date the subject signed.)
- The subject should receive back a full-signed copy of the consent form for their records.

*The above guidance applies when the IRB has required the subject's signature on a paper consent form. For minimal risk studies, other methods can be used to obtain and document informed consent and must be detailed in the study application, preferably the study protocol. If not previously approved, the IRB must approve the new electronic consent process as a study modification.

Informed Consent from Patients in Isolation
In response to the COVID-19 pandemic, it is recommended that study teams switch their consenting process from an in-person interaction to obtaining consent through remote means. For isolation patients in research requiring a signature, investigators/study teams have the following option for obtaining Informed Consent and Authorization:

- Consider electronic informed consent if available (Use of Electronic Informed Consent Questions and Answers)
    - For research that is FDA-regulated, electronic signatures must be obtained through software that meets the requirements of 21 CFR Part 11.
- If consent cannot be obtained electronically, consider these steps:
    - Provide consent form to patient from a healthcare worker who has entered the room
    - If direct communication with patient is not possible, investigator (or designee) can arrange a three-way phone or video call with patient, an impartial witness, and (if desired and feasible) additional persons as requested by the patient
    - A standard process for such calls should be used that involves a series of steps for confirmation, which must be documented in the IRB Submission Application (either New or Amended) – see Guidance for details
    - If the consent document cannot be collected from the patient's location, options include attestation by witness or photo of the signed informed consent document.

It is the Principal Investigator's responsibility to submit a detailed plan to the IRB on how Informed Consent will be obtained for patients in isolation.

21. REQUEST FOR USE & DISCLOSURE OF PROTECTED HEALTH INFORMATION

The UMC IRB shall serve as the UMC's Institutional Privacy Board for purposes of compliance with all applicable requirements of the Health Insurance Portability and Accountability Act (HIPAA). HIPAA requirements shall apply to all Protected Health Information (PHI). In general, HIPAA requirements will apply to Research and Research-related activities that involve Identifiable Health Information being created by, received from, or shared with a health care provider, clinical researcher, or another employee or agent of a unit of a UMC Covered Component that is performing Covered Functions for or on behalf of the UMC Covered Component.

Under HIPAA, PHI has one or more of the following identifiers associated with it: 1. Names; 2. All geographical 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, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Phone 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, including license plate numbers;
13. Device identifiers and serial numbers;
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; and
18. Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)

Other Applicable Privacy Laws: In some cases, privacy laws other than HIPAA may apply to data used for Human Subjects Research (e.g., the Family Educational Rights and Privacy Act may apply to research using educational records). In such cases, the IRB shall follow the requirements of applicable laws regarding acquisition, use and disclosure of data.

PROCEDURES:

Research to be Reviewed for Compliance with HIPAA Regulations: Any Research that is subject to the jurisdiction of the UMC IRB shall be reviewed to determine if the HIPAA Regulations apply, and, if applicable, to ensure compliance with the HIPAA Regulations. In addition, the UMC IRB shall review any request for the use or disclosure of PHI for Research purposes, and any and all requests involving the use of UMC's non-public information to identify or contact Human Subjects or prospective Human Subjects.

Standard of Review: In reviewing any Research matters involving the use or disclosure PHI, the IRB will make a determination as to whether the use or disclosure requires (a) Authorization by the Research participant or his/her Legally Authorized Representative; or (b) the grant of a partial or complete alteration or Waiver of HIPAA Authorization requirement.

Documentation to be Submitted to IRB for HIPAA Review: In general, if a Researcher who works for a unit that is a part of an UMC Covered Component, or who wants to receive PHI from a unit that is an UMC Covered Component, he/she must have a HIPAA Authorization document signed by the subject whose information is to be used/disclosed; or, the IRB may grant a Waiver of HIPAA Authorization if the study meets certain criteria; or, the Researcher may provide information to the IRB to establish another means under the HIPAA regulations for gaining access to the PHI (e.g., Research regarding decedents' information, Research involving a Limited Data Set and Data Use Agreement, etc.). Accordingly, such Researchers must either submit a HIPAA Authorization form to the IRB for review, or submit an application for a Waiver of HIPAA Authorization for IRB consideration, or provide information that substantiates why another provision of the HIPAA regulations will permit use or disclosure of the PHI.
The UMC IRB has the authority to determine whether a HIPAA Authorization is required; to determine to what extent the Researcher may have access to, use or disclose health information regarding subjects; and/or to determine whether to grant a Waiver of HIPAA Authorization. The IRB will not grant a Waiver of HIPAA Authorization or permit access to PHI for review until adequate information to assess whether the access and/or use meets the criteria for waiver is obtained.

HIPAA Authorizations for Research: The UMC IRB will post on its website for use by Researchers template language to be used for an Informed Consent and HIPAA Authorization. Researchers are advised to use this template language. In

evaluating any HIPAA Authorization language that is submitted for review, the IRB will review the HIPAA Authorization to make sure that it meets each of the following criteria:

The form is written in plain language and states that the person who signs the form will be provided with a copy of the signed document and that the Researcher and the UMC Covered Component that provides any PHI to the Researcher also will retain a copy of the document as required by HIPAA.

A description of the PHI to be used or disclosed that identifies the information in a specific and meaningful fashion.

The name or other specific identification of the person(s) or class of persons, authorized to make the requested use or disclosure.

The name or other specific identification of the person(s), or class of persons, to whom the PHI will be disclosed or by whom it will be used.

A description of each purpose of the requested use or disclosure; provided, however, that as of January 25, 2013, the description of purpose no longer needs to be study specific. The Authorization must include a description of each purpose of the requested use or disclosure of PHI, including a description of any use or disclosure for future Research purposes.

The description of the future Research purposes must provide reasonable notice to the individual that would cause him/her to expect that his/her PHI will be used or disclosed for the described future Research purposes.

An expiration date or expiration event that relates to the person whose PHI is requested, or the purpose of the use or disclosure of the PHI. Note: The statement "end of the research study, "none," or similar language is sufficient if the authorization is for a use or disclosure of PHI for Research, including for the creation and maintenance of a Research database or Research repository.

The signature of the individual study subject and date, or if the HIPAA Authorization is to be signed by a legally authorized representative of the individual, the representative's signature along with a statement of the representative's authority to act for such individual (e.g., parent, legal guardian, etc.).

A statement of the study subject's right to revoke the HIPAA Authorization in writing along with a description of how the study subject may revoke the Authorization and the IRB-approved and/or HIPAA permitted exceptions to the right to revoke.

A statement that the provision of Research-related treatment may be conditioned on the provision of an HIPAA Authorization for the use or disclosure of PHI for such Research, along with a statement of the consequences to an individual for refusing to sign an Authorization in such circumstances.

A statement of the potential for information disclosed pursuant to the HIPAA Authorization to be re-disclosed by the person(s) who receive the information and who are not covered by HIPAA, thus rendering the information unprotected by HIPAA requirements.

Compound Authorizations: As of January 25, 2013, some compound Authorizations that combine certain conditioned and unconditioned Authorizations for Research are permitted. A "conditioned Authorization" is an Authorization that conditions the provision of treatment, payment, enrollment in a health plan or eligibility for benefits (e.g., obtaining a Research only treatment in the context of a clinical trial) upon signing the Authorization to permit certain uses and disclosures of PHI (e.g., disclosure of the PHI to the Sponsor of the clinical trial). A "compound Authorization" is one

that combines Authorization of the use or disclosure of PHI for the conditioned purpose (e.g., receiving Research only treatment in the context of a clinical trial) with use or disclosure of PHI for a separate purpose (e.g., optional biospecimen banking) that is not required to obtained the conditioned treatment, payment, enrollment or eligibility. The Authorization for the use or disclosure of PHI for a Research study may be combined with any other type of written permission for the same or another Research study provided that the following requirements are met:

(a) the Authorization must clearly differentiate between the conditioned and unconditioned components;
(b) the Authorization must provide the individual with an opportunity to affirmatively opt-in to the Research activities that are described in the unconditioned component; and
(c) an Authorization for the use or disclosure of Psychotherapy Notes can only be combined with another Authorization for the use and disclosure of Psychotherapy Notes.

Prohibition on Sale of PHI: The sale of PHI (including PHI contained in a Limited Data Set) by UMC for research purposes is generally prohibited; However, UMC may calculate and receive reasonable cost-based fee that covers that cost of preparing and transmitting PHI for research purposes.

Criteria for Waiver of HIPAA Authorization: In certain circumstances, the UMC IRB may grant a complete or partial Waiver of HIPAA Authorization requirement and permit a Researcher working in or receiving information from a unit that is a part of an UMC Covered Component to access PHI without a subject's written HIPAA Authorization. The IRB will not grant an alteration or Waiver of HIPAA Authorization, in whole or in part, unless the Researcher has submitted an application for the Waiver of HIPAA Authorization requirement that establishes that the following waiver/alteration criteria are met. Explanations as to how each of these elements is met MUST be included in the application:

The use or disclosure of PHI involves no more than minimal risk to the subject based on the presence of at least the following elements:

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

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

Adequate written assurances that the PHI will not be re-used or disclosed to any other person or entity, except as required by law for authorized oversight of the Research, or for other Research for which the use or disclosure of PHI is permitted under the HIPAA Regulations (e.g., certain Research conducted by governmental public health agencies).

The alteration or waiver will not adversely affect the privacy rights and the welfare of the individuals;

The Research could not practicably be conducted without the alteration or waiver (no reasonable opportunity to speak with the patient);

The Research could not practicably be conducted without access to and use of the PHI; and

The privacy risks to persons whose PHI is to be used or disclosed are reasonable in relation to the anticipated benefits if any to these persons, and the importance of the knowledge that may reasonably be expected to result from the Research.

Documentation of the Grant of an Alteration or Waiver of the HIPAA Authorization Requirement: If the IRB determines that a request for an alteration or waiver, in whole or in part, of the HIPAA Authorization requirement meets the foregoing waiver/alteration criteria then it may grant the alteration or waiver and provide the Researcher with

documentation of the approval. The PI is responsible for providing a copy of this documentation to the appropriate unit or person within that unit that is a part of an UMC Covered Component that will be providing any PHI for the Research, and a copy of the documentation also will be placed in the protocol file. The documentation provided by the IRB must include the following elements:

A statement identifying the IRB and the date on which the grant of the alteration or waiver of the HIPAA Authorization requirement occurred;

A statement that the foregoing waiver criteria have been satisfied;

A statement identifying whether the request for alteration or waiver was reviewed under normal review procedures or expedited review procedures;

A statement that briefly describes the PHI for which use or access has been determined to be necessary by the IRB, subject to the Minimum Necessary Rule (see below); and

The signature of the IRB Chair, or another member of the IRB as designated by the Chair.

Partial HIPAA Authorization Waivers: The IRB may grant a partial Waiver of HIPAA Authorization to allow access to PHI for the purpose of identifying potential subjects prior to subject enrollment. Once a potential subject has been identified, no further PHI may be reviewed or collected until the subject gives HIPAA Authorization at the time he/she decides to participate in the study.

Sample Forms: A sample application for a waiver of HIPAA Authorization is set forth on the UMC IRB website. Researchers who are granted a Waiver of HIPAA Authorization requirement should sign, and have all Research staff members who will have access to PHI sign, confidentiality agreements. A sample researcher confidentiality agreement is set forth on the UMC IRB website.

[**Reference**: 45 C.F.R. § 164.512(i)].

Minimum Necessary Rule: In determining the type and scope of the PHI for which the IRB determines use or access under a waiver or alteration of the HIPAA Authorization requirement is necessary, the IRB must limit access to only that PHI which is reasonably necessary to accomplish the purpose for which the request is made. For example, if the Research requires access only to certain test results in order to accomplish the purpose of the Research, the IRB should deny a request by the researcher for access to the entire medical record. If a UMC Covered Component is disclosing the PHI, it may rely on a researcher's documentation or representations that the information being requested is the minimum necessary PHI if the documentation/representations have been reviewed by the IRB and reliance is reasonable under the circumstances.

[**Reference**: 45 C.F.R. § 164.514(d)].

Accounting Rule: If a researcher who is a part of the UMC Covered Component obtains PHI for Research purposes pursuant to a waiver of the HIPAA authorization requirement, then the researcher must account for any subsequent disclosure that is made of the PHI. Records of disclosure should be maintained for six years after the disclosure occurs. A Human Subject may request the Researcher to provide him/her with an accounting of the persons to whom and purposes for which his/her PHI was disclosed.

Acceptable Method of Accounting for Disclosure of PHI for Particular Research Purposes: If a UMC Covered Component, or employee thereof, makes a disclosure of PHI to a Researcher for a particular Research purpose and the disclosure involves the PHI of 50 or more people (e.g., a disclosure of certain medical information from the records of 50 or more people to a Researcher for screening for subjects for a specific Research protocol), then the UMC Covered

Component/employee must keep an individual record showing the specific Research protocol or activity to which an Individual's PHI was disclosed OR it may use the following more general method of accounting for such disclosures:

List of Elements in Disclosure: For each of disclosure within this category, keep a record of: (1) the name of the Research protocol or other Research activity for which the disclosure was made; (2) a description, in plain language, of the Research protocol or activity, including the purpose of the protocol and the criteria for selecting certain records; (3) a description of the PHI that was disclosed; (4) the period when the disclosures were made, including the date of the last disclosure made within this period; (5) the name, address and telephone number of the entity that sponsored the Research and or the Researcher to whom the information was disclosed; and (6) a statement that the PHI of the Individual who is requesting the accounting may or may not have been disclosed for a particular protocol or Research activity.

Provision of List of Protocols Upon Request: If the general method of accounting is employed, then each individual who requests an accounting of the disclosure of his/her PHI in accordance with applicable HIPAA Regulations and UMC HIPAA policies shall be provided with a list of all Research protocols at UMC for which the PHI of 50 or more people was disclosed. This list shall contain all of the elements set forth above in the subsection entitled List of Elements in disclosure. In addition to providing this list of protocols (if any), the UMC Covered Component/employee also shall provide the individual making the request with an accounting of any other non-Research related disclosures of that individual's PHI or Research disclosures for fewer than 50 people, as required by applicable HIPAA Regulations.

Additional Assistance: If the UMC Covered Component/employee provides its accounting of disclosures for Research protocols in the format described above (i.e., providing a list of Research protocols to which an individual's PHI might have been disclosed, instead of providing a list of those protocols to which it actually was disclosed), then if it is reasonably likely that the individual's PHI was disclosed to a particular protocol or activity, the UMC Covered Component/employee must, upon the individual's request, assist the individual in contacting the Research Sponsor and Researcher involved in the protocol.

Right to Revoke HIPAA Authorization. A Research subject may withdraw consent to participate in a Research study in writing, verbally or by failure to further participate. However, under HIPAA, unless the informed consent/Authorization form states otherwise, HIPAA requires a subject to revoke his/her Authorization in writing in order to revoke the subsequent use or disclosure of his/her PHI. The Authorization is required to state that Research subject has the right to make a revocation of the Authorization in writing, along with stating any lesser means for revocation that may be permitted (e.g., verbal revocation). [NOTE: Even though an Authorization form may specify that the revocation of Authorization is to be in writing, if a verbal revocation is received, or if the participant verbally withdraws from the study, then the Researcher should not access any further PHI of the participant from that point on.]

Revocation of a Compound Authorization: Where it is clear from the Research subject's written revocation that only one part of a compound Authorization is being revoked, then the remainder of the Authorization may remain in effect. If the written revocation is not clear, however, then written clarification must be obtained from the Research subject as to which Research activities are in included in the revocation. If clarification is not forthcoming, then the revocation shall apply to all Research activities set forth in the compound Authorization.

Use of PHI After Withdrawal from Participation in a Study.

Withdrawal by Means Other than Writing. If the Authorization specified that revocation of Authorization was to be in writing, and a subject withdraws from participation in a Research study by any means other than in writing, then, when Authorized by the IRB, PHI that has been collected for approved Research purposes may be included in data analysis and study results, unless otherwise stated in the informed consent form/Authorization. [NOTE: The most cautious approach with regard to such data, however, is to

refrain from any further use or disclosure of the PHI except as is permitted in the sub-section immediately below.]

Withdrawal in Writing. Once a subject withdraws his or her Authorization in writing then no further use or disclosure of the subject's PHI is permitted except to the extent that the UMC Covered Component has taken action in reliance on the original Authorization. For example, if data was already collected in reliance on the Authorization, enough of the data can be disclosed to a study Sponsor to advise the Sponsor of the subject's revocation/withdrawal, and any data that was submitted to the Sponsor prior to the revocation does not have to be retrieved.

[**Reference**: 34 C.F.R. §§ 164.508 & 164.512].

Transition Period Provisions. PHI that was created or received before or after HIPAA's compliance effective date of April 14, 2003 may be used for the Research purposes for which it was obtained, if the PHI was obtained pursuant to one of the following means, and then, only to the extent allowed by the means by which it was obtained:

An Authorization or other express legal permission from an Individual to use or disclose PHI for the Research.

The informed consent of the Individual to participate in the Research.
A waiver by the IRB of informed consent for the Research; provided, however, that if informed consent is sought from an Individual after the HIPAA effective compliance date, then an Authorization must be sought and obtained as well.

Additionally, HIPAA authorizations and waivers of informed consent and authorization obtained prior to January 25, 2013, shall remain effective.

De-Identified Data, Limited Data Sets and Research: UMC's requirements for the Research use or disclosure of De-Identified Data or Limited Data Sets and described in the UMC HIPAA policies

Other Applicable Privacy Laws: In the event that the data used in a particular research is governed by laws other than HIPAA, the IRB shall seek the advice of General Counsel with regard to legal requirements regarding the acquisition, disclosure, or use of the data.

Reference: 45 C.F.R. § 164.532.

Applicable Regulations: See specific regulatory references above and see *Modifications to the HIPAA Privacy, Security, Enforcement and Breach Notification Rules Under HITECH and GINA; Other Modifications to the HIPAA Rules*, 78 F.R. No. 17, p. 5566-686 (January 25, 2013).

22. INVESTIGATIONAL DRUGS, DEVICES & PROCEDURES

Investigators who conduct human research regulated by the Food and Drug Administration (FDA) are required to know and comply with all relevant FDA regulations governing the use of investigational devices or other test articles. Investigators must also follow the guidelines given by UMC in regards to devices. If the primary intent of the investigational use of a test article is to develop information about the product's safety or efficacy, an Investigational New Drug (IND) or Investigations Device (IDE) may be required. If an IND or IDE is required, the investigator proposing to conduct the study must first obtain FDA approval of an IND or IDE application either directly or indirectly via a device or pharmaceutical sponsor. It is also the responsibility of the investigators to meet the requirements of regulations in 21 CFR 312 and 21 CFR 314 (investigational drugs) or 21 CFR 812 and 21 CFR 814 (investigational devices).

Definitions

Food and Drug Administration	The federal oversight agency responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
Investigational Agent	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. This includes products with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, products used for an unapproved indication, or products used to gain further information about an approved use.
Investigational New Drug (IND)	FDA granting of permission that a new drug, agent or biologic may be used in humans prior to FDA marketing approval. This FDA permission is evidenced by the assignment of an IND number by the FDA or the granting of an IND exemption.
Investigational Device	Any healthcare product that does not achieve its primary intended purposes by chemical action or by being metabolized. An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.
Significant Risk (SR) Device Study	Under 21 CFR 812.3(m), an SR device means an investigational device that: • Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or • Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
Nonsignificant Risk (NSR) Device Study	A device study that does not meet the definition for an SR device study.
Investigational Device Exemption	A FDA approved exemption that permits a device that otherwise would be required to comply with a performance standard or to have pre-market approval to be shipped lawfully for the purpose of conducting investigations of that device.
Emergency Use	The use of an investigational drug, agent, biologic, or device with a human subject in an immediate serious life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

Emergency Treatment IND	A mechanism through the FDA for providing eligible subjects with investigational drugs, agents, or biologics for the treatment of an immediate serious or life-threatening illness for which there are no satisfactory alternatives.
Emergency Treatment IDE	A mechanism through the FDZ for providing eligible subjects with investigational devices for the treatment of an immediate serious or life-threatening illness for which there are no satisfactory alternatives.

Investigational Use of Test Articles

An Investigational New Drug (IND) is required for investigational or experimental drugs if the drugs are being used for the purpose of developing information about their safety or efficacy. Approved, marketed drugs may also require an IND if the proposed use in research is different from the previously FDA-approved use, or administered by an unapproved route or method of delivery or an altered dose. An IND may not be required if it falls under an exemption.

A clinical investigation of a drug is exempt from the IND requirements if all of the following criteria for an exemption in 312.2(b) are met:

- The drug used in the research is lawfully marketed in the United States;
- There is no intent to report the investigation to FDA as a well-controlled study in support of a new indication and no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, does, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product. (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of § _312.7 (i.e. investigation is not intended to promote or commercialize the drug product).

For devices, an IDE may not be necessary if:

- The device is approved as a non-significant risk device (NSR)
- The device is used or investigated in accordance with the indications in labeling in effect at that time.
- The device has been determined by the FDA to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence.
- The device is classified as a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
  - Is noninvasive,
  - Does not require an invasive sampling procedure that presents significant risk,
  - Does not by design or intention introduce energy into a subject, and
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- The device is used for consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- The device is intended solely for veterinary use.

- The device is shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).
- The device is classified as a "custom device" as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Investigators will be asked on the IRB protocol application to indicate whether the research involves drugs or devices. If so, they will be asked if there is an IND/IDE for the research. If there is, they will be asked for evidence of the IND/IDE, which could be a:

- Industry sponsor protocol with IND/IDE
- Letter from FDA
- Letter from industry sponsor

If the research involves drugs or devices and there is no IND/IDE, the investigator will be asked for a rationale as to why it is not required.

Sponsors are responsible for making the initial risk determination whether a device study is Significant Risk (SR) or Nonsignificant Risk (NSR) and providing it to the IRB. The FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination.

The IRB will review protocols involving investigational devices to determine if the device is a "Significant-Risk device" (SR) or a "Non-Significant Risk" (NSR) device, although IRBs will not make the significant/nonsignificant risk determination if FDA has already made the determination.

Significant Risk (SR) Device Studies

- SR device studies must follow all the IDE regulations at 21 CFR 812.
- SR device studies must have an IDE application approved by FDA before they may proceed.

Nonsignificant Risk (NSR) Device Studies:

- NSR device studies must follow the abbreviated requirements at 21 CFR 812.2(b):
  - The device is not a banned device.
  - The sponsor labels the device in accordance with 21 CFR 812.5.
  - The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
  - The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.
  - The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.
  - The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21CFR 812.150(b) (1) through (3) and (5) through (10).
  - The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).
  - The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.
- NSR device studies do not have to have an IDE application approved by FDA.
- Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. This means that an IRB may approve an NSR device study and an investigator may conduct the study without FDA knowing about it.
- An IRB's NSR determination is important because the IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies. An NSR device study may start at the institution as soon as the IRB reviews and approves the study and without prior approval by FDA.

If the IRB determines that the research involves a SR device, an IDE is necessary unless it meets the exemption criteria in 21 CFR 812.2(c). If the Principal Investigator does not already have an IDE, the PI will be notified in writing that IRB approval is pending receipt of an IDE. Devices that do not meet the definition of a SR will be considered a NSR. If the IRB determines that the research involves a NSR device, no IDE is required. If an IRB determines that an investigation, presented for approval as involving a non-significant risk device involves a significant risk device, it notifies the investigator and, where appropriate, the sponsor.

Protocols involving an Investigational New Drug (IND) or Investigational Device Exemption (IDE) require consideration and satisfaction of the pertinent FDA and the federal HHS regulations (21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, and 45 CFR 46).

Protocols involving an IND or IDE will undergo initial and continuing review at a convened meeting using. The IRB meeting will include at least one licensed physician unless the protocol meets the criteria for expedited review (i.e., all treatment components complete, in follow-up only, data analysis only).

Consent for studies involving an IND and/or IDE will be obtained as stated in the UMC IRB – Informed Consent Section. FDA regulations allow waiver of consent if research meets the criteria specified in 21 CFR 50.23 or 21 CFR 50.24 and federal HHS regulations allow a waiver of consent if research meets the criteria specified in 45 CFR 46 "Waiver of Informed Consent Requirements in Certain Emergency Research." Otherwise, consent is required for all research that falls under FDA regulations or involves experimental treatment, tests, or drugs. In addition, the consent form will identify the test article as investigational and will inform subjects that the FDA may inspect research records.

The IRB must review the sponsor's SR or NSR determination for every investigational medical device study, unless the FDA has already made a determination of the type of risk category that the device falls under. If the IRB disagrees with the sponsor's classification, the device is subject to modification of the risk category.

Determination of Significant Risk-Investigational Devices

If the IRB determines that an investigation presented for approval under 21 CFR 812.2(b) (1) (ii) involves a significant risk device, the IRB will notify the investigator and, where appropriate, the sponsor. A "significant risk device" is defined as an item that:

- Is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject; or
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject; or
- Is for use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety and welfare of a subject.

If the IRB concurs with the sponsor and determines that the research involves a SR device, an IDE is necessary unless it meets the exemption criteria in 21 CFR 812.2(c). If the Principal Investigator (PI) does not already have an IDE, the PI will be notified in writing that IRB approval is pending receipt of an IDE. Devices that do not meet the definition of a SR will be considered a NSR. If the IRB determines that the research involves a NSR device, no IDE is required. If an IRB determines that an investigation, presented for approval as involving a non-significant risk device involves a significant risk device, it notifies the investigator and, where appropriate, the sponsor.

The IRB will make every attempt to obtain a final report from PIs at the close of a study.

University and Affiliate Research

UMC may rely on affiliate sites to control investigational or unlicensed test articles. The IRB requires investigators to submit affiliate policies for the storage, dispensing, handling, and disposal of investigational and FDA-approved drugs, agents, and biologics for review, unless the current version of affiliate's policies are already on the file with the UMC IRB.

23. EMERGENCY USE

A one-time emergency use of an investigational drug, device, or biologic "test article" by an investigator without prior IRB review and approval is permitted under 21 CFR 56.104(c). The UMC IRB allows the emergency use of an investigational drug if the FDA Requirements for emergency use are met. Whenever possible, the IRB Chair should be notified of the intent to use the investigational drug or biologic to ensure that the FDA requirements for emergency use are met.

When an investigator conducts an emergency use of a test article in a life-threatening situation without prior IRB review, the activity is research under FDA regulations and the patient is a subject under FDA regulations. The FDA may require data from an emergency use of a test article in a life-threatening situation to be reported in a marketing application. Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care for patients who need such care.

Definitions

Emergency Use	The use of an investigational drug, agent, biologic, or device with a human subject in an immediate serious life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.
Emergency Treatment IND	A mechanism through the FDA for providing eligible subjects with investigational drugs, agents, or biologics for the treatment of an immediate serious or life-threatening illness for which there are no satisfactory alternatives.
Emergency Treatment IDE	A mechanism through the FDA for providing eligible subjects with investigational devices for the treatment of an immediate serious or life-threatening illness for which there are no satisfactory alternatives.

Emergency Use

The federal HHS regulations at 45 CFR 46 does not permit research activities to be started, even in an emergency, without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient is not considered a research subject under the federal HHS regulations. Therefore, in order to comply with the federal HHS regulations, patients receiving emergency care under these conditions may not be accrued as research subjects, nor may resultant data be included in research [21 CFR Ch. 1, 50.23(a) and 56.102(d)] and Federal Wide Assurance FWA00002738 in Compliance with DHHS Regulations.

Emergency use of a test article [21 CFR 56.104(c)] is considered to be human research by the FDA. It meets the FDA definition of clinical investigation and requires regulation under the Food, Drug, and Cosmetic Act. Therefore, when an Investigator conducts human research that involves the emergency use of a test article in a life-threatening situation without prior IRB review, the activity is research under FDA regulations and the patient (as recipient of the test article) is a subject under FDA regulations. A retrospective report of the emergency use of test article in a life-threatening situation is allowed. However, this process must not be used to circumvent IRB review of a prospectively conceived systematic investigation designed to develop or contribute to generalizable knowledge.

Terms such as "interim," "compassionate," "temporary," or other terms for an expedited approval process will not be utilized for requests for emergency use of FDA-regulated products. The IRB must either grant approval at a convened full board meeting (may use the data for research), or if the conditions of 21 CFR 56.104(c) are met and it is not possible to convene a quorum within the time available, the emergency use may proceed without IRB approval.

Emergency Use of Investigational Drugs, Agents, or Biologics

The emergency use of investigational drugs, agents, or biologics will be handled in accordance with FDA regulations and institutional policies and procedures. Although 21 CFR 56.104(c) allows for an exemption from prior review and approval by the IRB for emergency use, UMC IRB requires prior notification of the IRB Chair or Chair's Designee of emergency use of investigational drugs, agents, or biologics. This is done in order to determine if the criteria allowing the exemption are met.

FDA regulations at 21 CFR 56.102(d), allows for one emergency use of an investigational drug, agent, or biologic without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. The only exception to this provision is if the IRB has not had sufficient time to convene a meeting to review a protocol.

Emergency Use of Investigational Devices

The emergency use of investigational (unapproved) medical devices will be handled in accordance with FDA regulations and institutional policies and procedures. Although 21 CFR 56.104(c) allows for an exemption from prior review and approval by the IRB for emergency use. UMC IRB requires prior notification of the Chair or the Chair's designee of emergency use of investigational (unapproved) medical devices. This is done in order to determine if the criteria allowing the exemption are met.

Subsequent emergency use of an investigational (unapproved) medical device may not occur unless the Investigator or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with the FDA and the FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist.

Manufacturers or sponsors that agree to allow the use of the investigational drug, agent, biologic or device, but will not ship without "an IRB certification (approval) letter", will be provided a written statement that the IRB is aware of the proposed use and based on the information it has been provided by the Investigator that the proposed use meets the requirements of FDA 21 CFR 56.102(d).

Procedures for the Emergency Use of FDA Regulated Test Articles

Investigator's Responsibilities

Requirements of the emergency use of investigational drugs, agents, or biologics:

- The emergency use of an investigational drug, agent, or biologic requires an IND.
  - The Investigator must contact the manufacturer of the drug, agent, or biologic first to determine if the test article can be made available for the emergency use under the manufacturer's IND or IDE; or
  - The need for an investigational drug, agent, or biologic may arise in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization must be made by the Investigator to the appropriate department at the FDA.

- Prior verbal notification to the UMC IRB of an emergency use followed by the submission of a letter from the Investigator which states the following:
  - The subject is in an immediate serious or life-threatening condition that needs immediate treatment;
    - Life-threatening means 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 end point 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 means 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.

- No generally acceptable alternative for treating the subject is available; and
- Because of the immediate need to use the drug, agent, or biologic, there is no time to obtain full board approval for the use.

- Even in emergency situations, the investigator is required to obtain informed consent from the subject or the subject's legally authorized representative unless both the investigator and an independent physician certify in writing all of the following:
  - The subject is confronted by a life-threatening (or severely debilitating) situation necessitating the use of the investigational drug;
  - ·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 legal representative; and
  - 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 listed above apply, the Investigator should make the determination and, within 5 working days after the use, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

Procedures following emergency use procedures for investigational drugs, agents, or biologics

The Investigator is required to:

- Submit a written follow-up report to the IRB within five (5) days of the emergency use of an investigational drug, device, or biologic. This report should include:
  - Name of the investigational drug, agent, or biologic;
  - Copy of the informed consent document;
  - Conditions under which the investigational drug, agent, or biologic was administered;
  - Date and time administered;
  - Subject protection measures;
  - Any adverse events or unanticipated problems to recipient or others; and
  - Outcomes, if known.
- Evaluate the likelihood of a similar need for the drug, agent, or biologic and if future use is likely, immediately initiate efforts to obtain IRB approval and an FDA-approved IND for the drug, agent, or biologic's subsequent use.

Requirements for emergency use of investigational (unapproved) medical devices

- The Investigator is responsible for justifying to the FDA that an emergency actually existed. To be considered an emergency the following criteria must be met:
  - The subject is in a life-threatening condition that needs immediate treatment;
  - No generally acceptable alternative for treating the subject is available; and
  - Due to the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

- The FDA expects the Investigator to determine the following:
  - Whether the criteria for emergency use have been met;
  - To assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist; and
  - Assure that the decision of the Investigator that an "emergency" exists is not based solely on the expectation that IDE approval procedures may require more time than is available.
- The Investigator must assure that the device developer notifies the FDA immediately after an unapproved device is shipped for an emergency use. An unapproved device may not be shipped in anticipation of an emergency.
- The Investigator is expected to follow as many human research protection procedures as possible. These include:
  - Obtaining a written independent assessment by an uninvolved physician;
  - Obtaining informed consent from the subject or the subject's legally authorized representative;
  - Notifying the IRB prior to the emergency use of the device who will notify institutional officials as applicable; and
  - Obtaining authorization from the IDE holder, if an approved IDE for the device exists.
- The Investigator is required to obtain informed consent of the subject or the subject's legally authorized representative according to 21 CFR 50 unless both the Investigator and a physician who is not otherwise participating in the clinical investigation certify in writing the following:
  - The subject is confronted by a life-threatening situation necessitating the use of the investigational (unapproved) medical device.
  - 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 legal representative; and
  - 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 listed above apply, the Investigator should make the determination and, within 5 working days after the use, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

Procedures following emergency use of investigational (unapproved) medical devices

- The Investigator is required to submit a written follow-up report to the IRB within five (5) days of the emergency use of an investigational (unapproved) medical device. This report should include:
  - Name of the investigational device;
  - Copy of the informed consent document;
  - Conditions under which the investigational device was utilized;
  - Date and time utilized;
  - Subject protection measures;
  - Any adverse device effects, adverse events or unanticipated problems to recipient or others; and
  - Outcomes, if known.
- The Investigator is to evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use.
- If an IDE for the use does exist, the Investigator is to notify the sponsor of the emergency use.
- If an IDE does not exist, the Investigator is to notify the FDA of the emergency use and provide the FDA with a written summary of conditions constituting the emergency, subject protection measures, and results.

IRB Responsibilities
The emergency use of FDA-regulated products requires the involvement of an IRB Chair (if the Chair is a physician) or the Chair's designee (who is an M.D.).

The IRB Chair or the Chair's designee will be promptly notified of the Investigator's intent for emergency use of an investigational drug, agent, biologic, or device. If there is no time to contact the IRB Chair, then the IRB Chair should determine whether the criteria allowing the emergency use was met retrospectively based on the report that is provided within 5 days and issue a letter as to whether the activity met the FDA criteria for emergency use. If on a retrospective review, the activity did not meet the criteria allowing an exemption, the action will be handled according to the UMC non-compliance section.

The IRB Chair or the Chair's designee will evaluate the Investigator's notification and guide the Investigator's adherence to the FDA regulations and institutional policies and procedures. The IRB Chair or the Chair's designee may request:

- An authorization from the sponsor or manufacturer to allow the use by the Investigator for the test article;
- An approved IND/IDE or a letter explaining exemption from the FDA;
- An adequate description of the situation regarding the use of the test article with an independent physician's certification, if applicable;
- The informed consent document or the certification for the exception from obtaining informed consent; and
- Any other materials that may aid in the evaluation of the request.

The convened full board will be notified of the emergency use of an FDA regulated product in the "Notification" section of the applicable IRB meeting agenda.

The IRB Chair or the Chair's designee will review the five (5) day follow-up report submitted by the Investigator.

IRB Staff Responsibilities
It is the responsibility of the staff member to facilitate any inquiries from Investigators regarding the emergency use of the FDA-regulated product.

The staff member will contact an IRB Chair or the Chair's designee to inform him/her of the Investigator's notification of emergency use.

The staff member will promptly notify the Director of an investigator's notification for emergency use of an FDA-regulated product.

The staff member will assist the Investigator in providing the appropriate documentation prior to the emergency use, if possible, and follow-up with the Investigator if an adequate written report is not received within 5 days following the emergency use.

The staff member will assist in a generating a letter (signed by the IRB Chair or Chair's designee) acknowledging notification of emergency use of the test article. The letter does not indicate IRB review or approval.

The staff member will update the IRB database accordingly.

Pharmacy Responsibilities
Any investigational drug, agent, or biologic utilized in an emergency use setting must be dispensed through the organization's or the affiliate's pharmacy, unless alternate procedures are necessary and are approved by the IRB Chair.

Although the UMC IRB does not have to prospectively review the emergency use of an unapproved device in a life-threatening situation, whenever possible, investigators are required to contact the UMC IRB and complete a form to document that an emergency exists.

Investigators are required to submit a report on the emergency use to the IRB within 5 working days. The report is reviewed by the IRB Chair to ensure that the emergency use meets FDA regulations. The investigator is informed that is he/she anticipates the need to use the investigational device in additional subjects, prospective review by the IRB is required.

24. HUMANITARIAN USE DEVICE (HUD)

A Humanitarian Use Device (HUD) is one that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States in a calendar year. The FDA office of Orphan Products Development (OOPD) determines if a device meets specific requirements, including scientific rationale and population prevalence, for designation as a HUD. Such devices may only be used in institutions where a local IRB has approved the use of the device to treat or diagnose the specific rare disease. IRB approval is needed to ensure that there are provisions in place that allow for the subject to understand that the safety and efficacy of the device is unknown at present.

The Food and Drug Administration (FDA) is authorized to exempt a Humanitarian Use Device provided that:

- The device will be used to treat or diagnose a disease or condition affecting fewer than 4,000 individuals in the United States,
- The device would not be available unless the exemption were granted,
- There is no comparable device available, and
- The device will not expose patients to an unreasonable or significant risk and the probable benefit to health outweighs the risks from use.

Treatment with a Humanitarian Use Device is subject to full board initial and continuing review by the IRB. At the time of review, the IRB will determine if written consent from subjects for use of the HUD or a waiver of informed consent is necessary.

If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, the Principal Investigator is required to provide written notification of the use to the IRB Chair within five working days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use.

It is the responsibility of the Principal Investigator to notify the FDA if the IRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five working days of notification of the withdrawal of approval.

Principal Investigators are reminded that Humanitarian Device Exemptions (HDEs) are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB protocol application.

25. USE OF BIOLOGICAL SPECIMENS FOR RESEARCH

With the increased use of samples from tissue banks and repositories that may be used for genetic research and implications that this has on the individual and his/her family, new ethical and regulatory dilemmas regarding the distribution and use of materials in research projects have been created. These tissue banks and repositories may have been established for a variety of purposes, ranging from clinical evaluation and diagnosis, to the use of discarded

materials, or to the use of samples collected specifically for research purposes. Consequently, the research implications may not have been addressed at the time that the sample was added to the tissue bank or repository.

While it is important to realize that samples from these tissue banks and repositories may be used in genetic research. It is also important to remember that non-genetic research is also being conducted that would have less effect upon the perceived risk to the subject and his/her family. Therefore, the method that the IRB would appropriately use to evaluate the research and determine whether informed consent is required may vary depending upon the protocol. Unfortunately, the purpose of the specific protocol may not be known at the time that the samples are being added to the tissue bank or repository.

The IRB is not responsible for reviewing protocols developed strictly for clinical care. However, research protocols are often proposed that involve the use of samples from tissue banks and repositories developed for clinical activities. Consequently, the procedures used to add samples to these collections may affect the way that the IRS can approve a proposed project.

Definitions:

Genetic Research
Research (not diagnostic testing), which involves either:

1. The analysis of human chromosomes or DNA from an individual and/or family members for the purpose of deriving information concerning the individual or family about the presence, absence or mutation of genes. DNA markers or inherited characteristics or
2. Other studies with the INTENT of collecting and evaluating information about heritable diseases and/or characteristics within a family

Prospective Study
This is a study in which the collection of tissue will occur "in the future"- in other words the biological specimen is not 'on the shelf' when approval for the research under review is requested. This may refer to:

1. Tissue that will be obtained specifically for research purposes after the research protocol has been approved by the IRS wherein the subject is asked to undergo a procedure to obtain a specimen for research purposes
2. Specimens to be collected from discarded clinical samples that will be obtained after the research is approved by the IRB

Retrospective Study
Retrospective research studies are studies that utilize existing tissue that has already been collected when the IRS request for approval is made. This may refer to:

1. Tissue collected for clinical indications and then stored (i.e. pathology specimens, left over sera. etc.) or,
2. A secondary use of tissue collected previously for another research protocol (i.e. material in a tissue bank)

Anonymous Samples
Biological specimens obtained by an Investigator without any Identifying information and without a link to an individual subject source.

Identified Samples
Biological samples obtained by an investigator or a 3rd party, which have identifiers attached or a link permits determination of the individual subject source through the use of a code.

Identifiers
The name, medical records number or social security number of an Individual subject.

Policy
There are two conditions under which use of tissue for research becomes an IRB Issue: *retrospective* use of previously stored tissue and *prospective* studies requesting the use or storage of tissue for current and/or future research. Similarly, there are two categories of specimens: those obtained initially for clinical or diagnostic purposes only, and those obtained for research purposes. IN ALL CASES, A PROTOCOL DESCRIBING THE PROPOSED RESEARCH USE OF THE SPECIMENS MUST BE SUBMITTED TO AND APPROVED BY THE IRB BEFORE THE TISSUE IS USED.

In the case of Exempt protocols, an investigator must obtain concurrence for the exemption from either the IRB chair or from an official who has been authorized by the IRB chair to review presumably Exempt protocols. Investigators cannot proceed, with a presumably exempt study without the concurrence of an IRB official. (See section on Exempt protocols).

The following information provides guidelines to help investigators better identify the appropriate process and level of review needed for a particular protocol. (Refer to tables on page 65)

1) *Retrospective studies* of already stored specimens must obtain IRB approval. The level of review and issues of informed consent may depend on the following:
   a) If samples are to be used **anonymously** (without linkage to subject identifiers), an investigator may request an exemption from full board review of a research protocol (see section on Exempt protocols and Table 1 on page 34).
   b) If samples can be **linked to identifiers either by the principal investigator or a third party**, then such protocols will require full board review or may be expedited. (see section on Expedited Review and Table 1 on page 34) Depending on the nature of the protocol, the investigator may be required to obtain informed consent from the patients for the new use.

2) *If prospectively* collected specimens are to be used for research purposes that are described. In a current protocol, then the protocol must have IRB approval before they are collected and used. Some studies may qualify for Expedited Review (see "Expedited Review") but most will require full board review (See Table 2). If the investigator plans to store specimens from this protocol for future research use, the use must be specified and justified and be included in the consent form if the future use cannot be specified, or is significantly different from the original plan, then the specimens' use. In future protocols must be approved by the IRB before the specimens are used. The investigator may be required to re-contact all of the subjects before their specimens can be used in this or any subsequent study.

3) *If prospectively* collected specimens obtained for clinical or diagnostic purposes are to be used for research purposes, then the specimens' use in future Protocols must be approved by the IRB before the specimens are used. Biological waste and left over specimens are included in this category. None of these studies will qualify for Exempt status, but will require either expedited or full board review. Depending on the nature of the protocol, the investigator may be required to obtain informed consent from the patients for the new use (See Table 3).

Informed Consent

The regulations governing the consent process for research in human subjects, described in 45 CFR 46.116-117, apply to research protocols involving stored tissue whenever it is necessary to obtain informed consent as deemed necessary by the IRB's policies. In addition, for the prospective storage of human tissue, the consent form must necessary contain the following information (as appropriate to the individual protocol):

1) Procedures that will be used to protect the confidentiality and privacy of any personal identifiers that will be associated with the source of a tissue sample or cell line;
2) Information about the control and ownership of tissue samples during storage;
3) The subject's right to withdraw his/her consent at any time either by requesting that the tissue be destroyed or that all personal identifiers be removed;
4) Information about the length of storage;
5) Whether the subject can obtain future access to the stored samples for information that may be of clinical relevance to him/her. Similarly, subjects must be told if such information will not be available in the future (e.g., because personal identifiers are to be removed);
6) How the investigator will handle future third-party access;
7) Information about possible secondary use of the stored tissue, or the possible creation of an immortalized cell line based on the specimen.

Special Considerations

Marketable Specimen

There may be situations where a patient or research subject is known to possess biologic materials with unique characteristics thought to have commercial value. In this case, if specimens are to be collected for research purposes and the Investigator expects that they will be commercialized into a marketable product or sent to a commercial sponsor for development, the consent form must state this possibility. IRB policy requires that the consent form stipulate that University Medical Center, Las Vegas, does not intend to share with the subject any financial or proprietary interest that may result from research on the subject's biologic sample.

Genetic Research

It is important for the investigator and IRB reviewers to consider whether the results of proposed genetic research could harm the subject or his/her family members in the future. Geller et al, reported that (1) genetic Information may affect an *entire family;* (2) genetic information *may* have symbolic *meaning* to the individual, the family or to the entire culture as a unique determinant of future health and behavior; (3) because of its probabilistic nature and potential for labeling patients, genetic information raises somewhat unique concerns from a social perspective, and (4) at present, the main risks and benefits of genetic research may be psychological and social rather than physical. (Geller et al. JAMA, 1997:227, 1468.) Therefore, the issue of confidentiality becomes paramount and the investigator should detail the steps that will be taken to prevent misuse of the subjects' records.

Exempt from Review

The Human subjects' materials are exempt from review if:

1) The samples are publicly available;
2) The samples are not identified;
3) The subject is deceased; (this may require Privacy board review or permission from a person with legal authority to act on behalf of decedent or the estate)
4) The process of unlinking the sample is sound and unachievable.

Expedited Review

The research is eligible for Expedited Review provided:

1) It is contained within one of the categories on the Expedited Review List (45 CFR 46) issued by the Department of Health and Human Services;
2) In its entirety, does not involve greater than minimal risk to the subject or group.

Use of Biological Specimens for Research IRB Review Tables

Retrospective Studies				
TABLE 1				
(Specimens already exist, have been collected and stored at the time of the IRB approval)				
Research on Stored Human Biological Specimens				
		GENETIC*		**NON GENETIC***
Consent	***Subject Identity***	***IRB Review***	***Consent***	***IRB Review***
No	Anonymous	Exempt**	No	Exempt**
Maybe	Identifiers Known to 3rd Party ONLY	Full/Expedited**	Yes	Full/Expedited**
Maybe	Identifiers Known to P-1	Full	Yes***	Full/Expedited**
**See definitions*				
***See expedited or exempt criteria*				
****Consent for banking specimen must be obtained. Protocol for future use of banked specimen must be submitted to IRB. Consent may or may not be required by IRB.*				

Prospective Studies				
TABLE 2				
(Prospective studies do not qualify for exemption)				
Biological specimens obtained prospectively and procedures performed exclusively for current and future research.				
		GENETIC*		**NON GENETIC***
Consent	***Subject Identity***	***IRB Review***	***Consent***	***IRB Review***
Yes	Anonymous or Unknown	Full	Yes	Full or Expedited**
**See definitions*				
***See expedited criteria*				

Prospective Studies				
TABLE 3				
Biological specimens obtained for clinical purposes to be used subsequently for correct research or banking for future research (includes biologic waste and left over specimens)				
		GENETIC*		**NON GENETIC***
Consent	***Subject Identity***	***IRB Review***	***Consent***	***IRB Review***
***	Anonymous	Expedited**	***	Full/Expedited**
***	Identifiers Known to 3rd Party ONLY	Full	***	Full/Expedited**
***	Identifiers Known to P-1	Full	***	Full/Expedited**
**See definitions*				
***See expedited criteria*				
****Consent may or may not be required by IRB. Consent for banking specimen must be obtained. Protocol for future use of banked specimen must be submitted to IRB.*				

26. GENETIC/DNA ANALYSES ON BLOOD OR TISSUE

When genetic DNA analyses will be performed on the blood or issues of subjects in a research study, the following points should be considered in all genetic research protocols. The investigators should specifically address the following {some may not be relevant to any particular study):

Recruiting Subjects

1) Does the proposed study population comprise family members? Has the appropriateness of various strategies for recruiting subjects (e.g., recruiting by other family members, by the investigator, through support groups, or through prospective subjects' personal physicians) been considered? Does the proposed strategy for recruiting subjects sufficiently protect prospective subjects from the possibility of coercion or undue influence?
2) Does the investigator plan to use clinical medical records as a source of research data about other persons (e.g., other fancily members)? If so, must their consent be obtained before their data can be included, or is the permission of the person providing the information sufficient?
3) Will the possible psychological and social risks of genetic research be adequately considered in the Consent process? Will appropriate counseling be provided as part of the consent process?

4) Will vulnerable populations (e.g., children, person with impaired mental capacities) be adequately protected? Under what circumstances can a research subject serve to grant permission to involve a minor child or an incapacitated adult in a study?
5) As science advances, other gene(s) might be found which may relate to the condition at hand. Another investigator may ask to use the cell line(s), without the patient's knowledge or consent. Therefore, the investigators need to specify what will happen to the blood and DNA. The subject MUST be informed about the possible uses of this material.
6) Generally, it has been recommended that subjects in genetic research be told what will happen to their DNA and/or cells. Will they be available for future studies or not? Will it be destroyed after the study is completed or not? There are a number of scientific reasons why it would be better if the DNA be kept. However, there are implications to the patient if other genes associated with the condition are discovered and the investigators have lost the ability to inform the patient of new findings that might affect his/her health.

Subject Confidentiality

1) Do the investigator's publication plans threaten the privacy or confidentiality of subjects? Has adequate consideration been given to ways in which subject's privacy and confidentiality can be protected (e.g., providing for consent to publication of identifying information)?
2) Will the data be anonymous? Will anyone be able to link the results from individual samples to a patient's identity? How anonymity will be maintained should be clarified. It is recommended that for blood/DNA sent outside the institution, the investigators will be dealing only with a subject's code number.
3) A major risk of participation in this study is a potential breach in confidentiality. The subject may be found to have a propensity for a disease or a condition which may have implications for medical insurance, life insurance, etc. How confidentiality will be maintained should be specified. In addition, subjects should be informed to what extent confidentiality will be maintained. This should be outlined in the POTENTIAL RISKS section of the consent. The risks if this information inadvertently gets out should be specified as well.
4) If a subject is found to have the disease or condition, or a propensity for the disease or condition under study, what are the implications for family members? Will they be tested? Will they be offered testing? How can this be done without compromising the confidentiality of the index subject's genetic studies?

Sample Use

1) Have adequate provisions been made for protecting against misuse of tissue samples (e.g. confidentiality obtaining consent for any use not within the original purpose for which the samples were collected)? What agreements with subjects are necessary to use, stored materials for new studies or for clinical diagnoses?
2) Have adequate provisions been made for the treatment of data and tissue samples in the event of subject withdrawal from the study?
3) When DNA analysis will be performed on blood or tissue, there should a description about what will happen to the blood sample. Possibilities include: 1) the blood could be discarded after the study; 2) the DNA could be saved in a freezer, and perhaps could be used by the same or a different investigator or in the future, with or without the patient' knowledge or consent; or 3) the cells could be used to immortalize a cell line, which might be used by the investigator or others for a variety of purposes with or without the patient's knowledge or consent.
4) When DNA from blood or tissue will be analyzed by a Laboratory different from the investigator (i.e., outside CHLA), a letter or memo from the investigator to the Laboratory where analysis will be performed, should be submitted with the CCI application. This should confirm what the CTILA investigator said would happen to DNA after analysis (i.e., will be discarded; will be saved for future studies, cell lines will be created, etc.).
5) There is the possibility of intellectual property rights stemming from the research. These may result in financial gain to someone other than the subjects. Is there a possibility of commercial value being derived from the blood or tissue? If so, will subjects stand to benefit from such commercial applications? If so, to what extent or with what limits? If not, this should be clearly stated in the study consent.

Information Disclosure

1. Has the investigator established clear guidelines for disclosure of information, including interim or inconclusive research results, to the subjects? Will subjects be informed in clear language; about what information they are entitled to receive at what point in the research? Will subjects receive an explanation of the meaning of the information they receive?
2. Will family members be protected against disclosures of medical or other personal information about themselves to other family members? Win they be given the option not to receive information about themselves? Will limits on such protection be clearly communicated to subjects, including obtaining advance consent to such disclosures (e.g., when family members will be warned about health risks).
3. Will appropriate counseling be provided, both as a part of the consent process and when communicating test or other research results to subjects?
4. Will subjects be informed about the possibility that incidental findings may be made (e.g., paternity, disease or conditions other than those under study)?
5. Will data be protected from disclosure to third parties, such as employers and insurance companies? Will the data be stored in a secure manner'? Will the data be, coded so as to protect the identity of subjects? Is a request for an NIMH *Certificate of Confidentiality* appropriate?
6. Does the investigator plan to disclose research findings to subjects' physicians for clinical use? Are such plans appropriate? Will the possibility of such disclosures be discussed with, and consented to by, prospective subjects?
7. Will subjects be informed of the results of the study? How will this occur? Should this be done in a way that does not appear in the subject's medical record? Informing the primary physician, for example, may cause data to be filed in the medical record, which could be subpoenaed. Therefore, the investigators should consider if it is appropriate that the results of this research NOT appear in the medical record.

27. DATA SAFETY MONITORING PLAN (DSMP) & DATA SAFETY MONITORING BOARD (DSMB)

The UMC IRB may require investigators proposing greater than minimal risk research with human subjects to address plans for monitoring the data to ensure the safety of subjects. The plan may be described by the sponsor in the corporate or cooperative group protocol or by the investigator in an investigator-initiated protocol. The DSMP must be presented in sufficient detail for the IRB to determine whether it is appropriate for the research.

Data and Safety Monitoring is the process for reviewing accumulated outcome data for groups of subjects to determine if the research should be altered or stopped. Ongoing review of the aggregate data to ensures that the study can continue without undue risk to participants. *Safety monitoring* also includes the continual assessment of risks and benefits through the review of individual adverse events and other safety parameters as they occur during the study to determine whether individual participants can safely continue to participate. *Data monitoring* is the process for ensuring the scientific integrity of the research data including its accuracy, completeness and its collection in compliance with the protocol.

A Data and Safety Monitoring Plan is unique to the trial and should be commensurate with the potential risk and with the size and complexity of the trial. Appropriate DSMPs may fall anywhere along a continuum from monitoring by the principal investigator or group of investigators to the establishment of an independent Data and Safety Monitoring Board (DSMB). Regardless of the type of DSMP, the individuals participating in the monitoring plan must be objective.

In general, a DSMB is the most appropriate way to monitor data and safety for studies that involve:

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
- There are *a priori* reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- There is prior information suggesting the possibility of serious toxicity with the study treatment;

- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- The study is large, of long duration, and multi-center.

The UMC IRB considers the following points when assessing the plan for monitoring the data:

- How will the trial be monitored? Will there be an independent data and safety monitoring board?
- How will decisions about stopping the trial be made? By whom? On what basis?

A DSMB charter will be utilized to define the responsibilities of the DSMB, define the procedures used to carry out these responsibilities and define the membership. The DSMB charter will be utilized whenever the UMC IRB has determined that the use of a DSMB is needed.

Definition
Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during, the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

28. PERFORMANCE IMPROVEMENT/QUALITY MANAGEMENT

The primary responsibility for quality management of research protocols rests with the principal investigator and the research team. Internal assessments performed by the Institutional Review Board supplement those quality management activities performed by the Principal Investigator and his/her research team.

It is the expectations of the UMC IRB that it's Investigators adhere to the highest standards of ethical and professional conduct in accordance with federal and state regulations and UMC institutional and IRB policies governing the conduct of research involving human subjects. If in the judgment of the IRB Chair or IRB Vice-Chairman that an investigator is not complying with the regulations and policies described in this document, receives an allegation and makes a determination as to the truthfulness of the allegation, the IRB Chairman or Vice-Chairman may request additional information or request that an audit of the research be performed.

Types of Audits:

For Cause Audits: If information is presented to the IRB raising serious concerns for patient safety and well-being or investigator non-compliance with IRB requirements, the IRB Coordinator will conduct a For Cause Audit. "For Cause" audits may be conducted without notice to the principal investigator.

Indicators for Audits
Indicators may include but are not limited to the following:

- Research participant/family member complaint
- Participant Death
- Investigator-driven studies with no DSMB
- Studies without identified oversight
- Lapses in continuing review/studies administratively closed by IRB
- Appearance of lack of staff support/resources/high staff turnover
- Ongoing concerns of quality IRB/R&D Submissions
- Ongoing document processing concerns in IRB/R&D

Scope of Site Visit

Selected subjects' research records and medical records, where necessary, will be reviewed to assess whether the research is being conducted in accordance with the approved study protocol, whether the consent process is appropriate and adequately documented, and whether adverse events and incidents are being reported to the IRB in accordance with institutional policies and procedures.

Investigator's Research Records
The investigator's research records will be reviewed to assess whether required documentation is present and organized and whether appropriate reports have been submitted to the IRB.

Process for Site Visit
The investigator will be notified by the IRB Coordinator that their study has been selected for a site visit. The investigator will be required to contact the IRB Coordinator within 3 working days to schedule the site visit within the subsequent 2-4-week period. The principal investigator and research coordinator must be available to answer questions during the site visit and both must be available for an exit interview.

Once the site visit is scheduled, the investigator is asked to provide a list of subjects enrolled, and prepares the essential files for review.

The IRB Coordinator selects 2-8 subjects whose research records will be examined.

- Small (1-10 subjects): 2 records selected
- Medium (11-25 subjects): 3-4 records selected
- Large (26-40 subjects): 5-6 records selected
- Very Large (>40 subjects): 7-8 records selected

At the end of the site visit, an exit interview is conducted, by one or more members of the site visit team, with the PI and research coordinator to review basic findings, answer questions from the researchers, provide education, and collect feedback on the IRB processes.

The IRB Coordinator, in consultation with the IRB Chair or Vice-Chair creates a written report detailing the findings of the site visit and making recommendations for improvement. Depending upon the nature of deficiencies found, the audit report may be discussed at the IRB meeting prior to being forwarded to the PI.

The report, with the addition of any IRB comments, if forwarded to the PI.

If necessary, the PI will be asked to provide a written corrective action plan to address any deficiencies noted in the report. In some cases, the PI's assurance regarding the immediate implementation of corrective actions recommended in the audit report will suffice.

Follow-up visits may be scheduled to see whether corrective measures, where necessary, have been successfully implemented.

29. UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Federal regulations, including those of the Department of Health and Human Services (DHHS) and the FDA, require institutions engaged in human subjects research to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any "unanticipated problems involving risks to subjects or others" (referred to as "unanticipated problems" in this policy) [45 CFR 46.103; 21 CFR 56.108]. In order to fulfill its obligations during the conduct of a research study, the IRB must receive from Principal Investigators and/or Sponsors information concerning unanticipated problems involving risk to human subjects in the study, including unanticipated problems not related to adverse events. Principal Investigators are required to report promptly to the IRB all unanticipated problems. In turn, the UMC IRB will

report unanticipated problems to the institutional official and OHRP in accordance with applicable federal regulations and IRB Policies and Procedures.

DEFINITIONS

Unanticipated Problems Involving Risks to Subjects or Others

Unanticipated problems include any event or other incident, experience, or outcome that meets **ALL** of the following criteria:

1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2) Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3) Suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Events

An ***adverse event*** is any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the drug or device being studied in the research or the subject's participation in the research.

FDA regulations use different terms when referring to an ***adverse event.*** For purposes of research regulated by the FDA the term "adverse event" means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. For example, *suspected adverse reaction* is used in 21 CFR 312.32 and is a subset of all adverse events (lesser degree of certainty about causality than adverse reaction); *adverse reaction* is used in 21 CFR 201.57(c)(7) for purposes of prescription drug labeling and are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

For investigational device exemption (IDE) studies, regulations use and define the term ***unanticipated adverse device effect (UADE)*** as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" 21 CFR812.3(s).

Adverse events encompass both physical and psychological harms and occur most commonly in the context of biomedical research, although on occasion, adverse events can occur in the context of social and behavioral research.

In the context of a multicenter study, adverse events can be characterized as either *internal adverse events* or *external adverse events*.

> ***Internal Adverse Event*s** are those adverse events experienced by subjects enrolled by investigator(s) at a UMC site or at a site in which the UMC IRB was the IRB of record. For example, if a subject enrolled at UMC experienced an event at a different medical facility, the event will still be considered an *internal* event. In addition, if another site relied on the UMC IRB for review (through an IRB Authorization Agreement), that site will be considered *internal*.
>
> > **NOTE:** For studies conducted under the **NCI CIRB Independent Model**, local-occurring reportable events should be reported to the NCI CIRB under the NCI CIRB Independent Model section of the UMC IRB Policies & Procedures.

External Adverse Events are those adverse events experienced by a subject enrolled by investigators at sites other than a UMC site or at a site in which the UMC IRB is not the IRB of record.

NOTE: External adverse events involving an UMC Sponsor-Investigator (i.e. multicenter where the UMC investigator holds the IND/IDE) - If the event occurred at an external site under the oversight of an UMC Sponsor-Investigator (UMC S-I), the event should be reported as if it had occurred at an ***internal*** site.

In the context of a single-center study, all adverse events would be considered *internal adverse events.*

In the case of *internal adverse events*, a local investigator typically becomes aware of the event directly from the subject, another collaborating local investigator, or the subject's healthcare provider. In the case of *external adverse events,* the local investigator learns of such events via reports that are distributed by the sponsor or coordinator center of the multicenter clinical trials. Reports of external adverse events represent the majority of adverse event reporting currently being submitted by investigators to the IRB.

Unexpected Adverse Event

For research regulated by the FDA (21 CFR 312.32(a)): An adverse event or suspected adverse reaction is considered **"unexpected"** if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current FDA application, as amended.

For research not regulated by the FDA, OHRP define unexpected adverse event as follows: Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

(1) The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

(2) The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Related or Possibly Related to the Research

Adverse events may be caused by one or more of the following:

(1) The procedures involved in the research;
(2) An underlying disease, disorder, or condition of the human subject; or
(3) Other circumstances unrelated to the research or any an underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be *solely* caused by (2) or (3) would be considered unrelated to participation in the research.

*For research not regulated by the FDA, OHRP defines **possibly related** as follows:* There is reasonable possibility that the adverse event may have been caused by the procedures involved in the research.

For research regulated by the FDA, a ***Suspected Adverse Reaction*** (21 CFR 312.32(a)) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and adverse event.

Serious Adverse Event

A ***Serious Adverse Event*** is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

(1) Results in death;
(2) Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
(3) Results in inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity;
(4) Results in a congenital anomaly/birth defect; or
(5) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(OHRP's modification from the definition of serious adverse event or serious suspected adverse reaction in FDA regulations 21 CFR 312.32(a).)

Prompt Reporting to the IRB

Investigators are required to ***PROMPTLY*** report to the IRB reportable events within 5 business days of event occurrence, or from when the investigator first learned about the event.

Periodic Reporting to the IRB

Investigators are required to ***PERIODICALLY*** report to the IRB reportable events at the time of annual or continuing review.

REPORTING REQUIREMENTS OF PRINCIPAL INVESTIGATORS

Principal Investigators (PI) are required to report the following reportable events ***PROMPTLY*** to the IRB:

1. **Unanticipated problems (UPs)** involving risk to subjects or others, including:
    a. Internal adverse events that are unexpected, related or possibly related to participation in the research and suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.
    b. External adverse events that have been determined to be unanticipated problems involving risks to subjects or others
    c. Other unanticipated events, or other incidents, experiences, or outcomes (not related to adverse events) that is related to the research and that indicates subjects or others
        i. Any event that requires prompt reporting according to the research protocol or plan or the sponsor.
        ii. Any accidental or unintentional change to the IRB-approved research protocol or plan that involved risks or has the potential to recur.
        iii. Any change to the research protocol or plan taken without prior IRB review and approval to eliminate apparent immediate harm or hazard to a research subject.
        iv. Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
2. **Unanticipated adverse device affect (UADE)** defined by 21 CFR 812.3(s).
3. In addition to unanticipated problems, the IRB requires that ***internal adverse events that result in death***, even if considered anticipated and not related to participation in the research, be report *promptly* to the IRB.

In a multicenter study or single-site study, the local investigator should assess whether the ***internal adverse event*** represents an unanticipated problem. If the local investigator determines that the adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB.

Regardless of whether the *internal adverse event* is determined to be an unanticipated problem, the investigator also must ensure that the adverse event is reported to a monitoring entity (e.g. the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

If the investigator determines that an *internal adverse event* is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event) the monitoring entity should report this determination to the investigator, and such reports must be *promptly* submitted by the investigator to the IRB.

External adverse events reports frequently represent a majority of adverse event reports submitted by investigators to IRBs. Reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter study to make meaningful judgments about whether the adverse events are unanticipated problems and in general, are not appropriately situated to assess the significance of individual external adverse events. In a multicenter study, it is clear that individual investigators and IRBs must rely on the sponsor to provide them information about adverse events occurring at other study sites. It is also clear that the sponsor receives adverse event information from all study sites and typically has more experience and expertise with the study drug or device than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of adverse event information from multiple sites and to make a determination about whether the adverse event is an unanticipated problem. Accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. The sponsor is expected to promptly provide the PI a report analyzing *External adverse events* and other potential *Unanticipated Problems.* The report should designate unanticipated problems, explain why an event constitutes an unanticipated problem, and set forth any protocol changes or other action to be taken in response to the UP. Sponsor IND and IDE safety reports should include such an unanticipated problem analysis. If the report fails to provide an explicit unanticipated problem determination, the PI will review the sponsor's external adverse event report and provide the IRB with a report designating which, if any, reported adverse events constitute an unanticipated problem, explaining the designation, and setting forth any protocol changes or other actions to be taken in response to the unanticipated problem. The IRB will consider the analysis provided by the PI and either request that the PI contact the sponsor to obtain an unanticipated problem determination for a specific event, or make its own determination. The UMC IRB has created a ***Reportable Event Assessment Tool*** and an ***Investigator Reporting Obligations to the UMC IRB Guide*** to aid the Principal Investigator determining the type of reportable event and the reporting requirements.

Reportable events listed above that must be ***PROMPTLY*** reported to the IRB must be reported using the ***Reportable Event Submission Form.*** The report shall include the following information:

1. Appropriate identifying information, such as (i) the title of the research protocol; (ii) the Investigator's name; (iii) the IRB protocol number; (iv) unique identifier for this event (v) subject identifier, (vi) date of event, and (vii) date of report.
2. Brief summary of the event, incident, experience, or outcome including the Description, Treatment, Outcome (including relevant dates) and Pertinent Subject History.
3. Why do you consider the event "Unexpected" in terms of nature, severity or frequency?
4. Why do you consider the event suggests that the research places subjects or others are at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized?)
5. What changes do you propose to the consent form and/or the protocol or specific corrective actions you have taken or will take in order to protect the rights, welfare and safety of the research subjects? If no changes to the consent form and/or the protocol are proposed, provide the rationale for why changes are not needed.

Principal Investigator should report the following reportable events ***PERIODICALLY*** to the IRB at annual review:

1. A summary of *internal serious adverse events or serious suspected adverse reactions* occurring in the previous approval period that are NOT determined to be unanticipated problems.
2. A summary of previously reported *unanticipated problems* (internal and external) that have occurred since the previous IRB approval period

The **Periodic Reportable Event Summary** is a sample spreadsheet that can be used for periodic event summaries.

Because most individual adverse events do not appear to represent unanticipated problems, the vast majority of adverse events reports, both internal and external, only need to be reported ***PERIODICALLY*** to the IRB.

External adverse events, or other incidents, experiences, or outcomes (not related to adverse events) and external deaths that are NOT considered unanticipated problems do NOT need to be reported to the UMC IRB promptly or periodically.

For any report of an external event determined not to be considered an unanticipated problem, the Principal Investigator should maintain a copy of the external adverse event report and documentation of the basis for this determination. This record is to be made available to the IRB or other authorized entities on request.

For further instruction, utilize the **Investigator Reporting Obligations to the IRB – UMC IRB Guidance form.**

Principal Investigator Reporting Obligations to Sponsors

The reporting requirements for the UMC IRB may differ from the reporting requirements for the sponsor. Investigators should report promptly to the UMC IRB **ONLY** the events that in the opinion of the investigator or sponsor **represent Unanticipated Problems involving risks to human subjects or others.**

Unnecessary reporting of events or problems that do not meet the criteria outlined above may impair the Board's ability to review and respond in a timely manner to actual situations where subject rights, welfare or safety are threatened. These reports will not be reviewed by the IRB and will be returned to the investigator.

The IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined above for prompt reporting. These submissions will not be reviewed by the IRB and will be returned to the investigator. Notify your sponsor of this policy. The IRB encourages study teams to communicate this policy to sponsors and should use this document for verification as necessary.

Unanticipated Problems (Not related to adverse events)

There are other types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. The incident, experience or outcome may have presented unanticipated risks to others (e.g., the sexual partners of the subjects, individuals the subject may come in contact with, family members, research personnel, etc.) in addition to the subjects. Some examples of Unanticipated Problems that Do Not Involve Adverse Events:

- *Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant*
- *Deviation from the protocol (protocol violation) that are related to participant safety, significant new findings, a defined subset of adverse events and IND safety reports*
- *Publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research*
- *A compliant of a participant that indicates an unexpected risk or cannot be resolved by the research staff;*

- *A breach of confidentiality*
- *Breach of privacy/confidentiality/data security/loss of study data/destruction of study data due to noncompliance,*
- *Incorrect labeling/dosing of study medication or test article*
- *Event that requires prompt reporting according to the sponsor*

In any case, an Unanticipated Problem that is Not an Adverse Event should be reported to the IRB only if it meets ALL of the three criteria defined for an unanticipated problem.

IRB REVIEW OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Once an unanticipated problem is reported to the IRB, the IRB Coordinator, in conjunction with the IRB Chair, reviews the report of the particular event and decides whether the event meets the definition of an unanticipated problem involving risks to subjects or others. Events that meet the criteria will be considered be considered unanticipated problems involving risks to subjects or others, will be reviewed by the convened IRB. IRB members will receive the report of the event and all other supplemental information.

The IRB or the IRB Chair has authority, under 45 CFR 46.109(a), to require, as a condition of continued approval by the IRB, submission of more detailed contextual information by the Principal Investigator, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event occurring in a research protocol.

Any proposed changes to the research study (e.g. study protocol and/or informed consent documents/ process) in response to an unanticipated problem must be reviewed and approved by the IRB before being implementation, except when necessary to eliminate apparent immediate harm or hazard to a research subject. Modifications to the study protocol and/or informed consent as a result of an unanticipated problem will be handled as follows:

1. If all proposed changes represent minor changes, the IRB Chair may review and, if appropriate, approve the modifications under an expedited review procedure.
2. If any of the proposed changes represent more than a minor change, or if the IRB Chair determines for any reason that he or she should not approve the proposed modifications under an expedited review procedure, the proposed modifications must be forwarded to the IRB for review at a convened meeting.

For multicenter studies, if the IRB or the IRB Chair proposes changes to the protocol or informed consent documents and/ or process in addition to those proposed by the study sponsor, coordinator center, or the local Principal Investigator, the IRB will request in writing that the local Principal Investigator discuss the proposed modifications with the study sponsor or coordinating center and submit a response or the necessary modifications for review by the IRB.

Possible actions that the convened IRB can take to manage unanticipated problems include:

1. Suspension of the research
2. Termination of the research
3. Notification of current participants (required when such information might relate to subjects' willingness to continue to take part in the research)

POLICY REFERENCE

- OHRP Guidance, January 15, 2007, "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events";
- FDA Guidance, January 2009, "Guidance for Clinical Investigators, Sponsors and IRB: Adverse Event Reporting – Improving Human Subject Protection;
- FDA Guidance, December 2012, "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies

30. INVESTIGATOR RESPONSIBILITIES

Principal Investigators are ultimately responsible for the conduct of research. Principal Investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

In order to satisfy the requirements of this policy, investigators who conduct research involving human subjects must:

- develop and conduct research that is in accordance with the ethical principles in the Belmont Report
- develop a research plan that is scientifically sound and minimizes risk to the subjects;
- have sufficient resources necessary to protect human subjects, including: supervision, a sufficient number of appropriately trained staff, and appropriate support services.
- protect the rights and welfare of prospective subjects;
- have plans to monitor the data collected for the safety of research subjects,
- have a procedure to receive complaints or requests for additional information from subjects and respond appropriately,
- ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating faculty and research staff;
- obtain and document informed consent as required by the IRB and ensuring that no human subject is involved in the research prior to obtaining their consent;
- ensure that all research involving human subjects receives IRB review and approval in writing before commencement of the research;
- comply with all IRB decisions, conditions, and requirements;
- ensure that protocols receive timely continuing IRB review and approval;
- report unexpected or serious adverse events to the IRB
- obtain IRB review and approval in writing before changes are made to approved protocols or consent forms
- seeking IRB assistance when in doubt about whether proposed research requires IRB review

Principal Investigators

At UMC, the following may serve as the Principal Investigator on a research project involving human subjects:

- physician staff members,
- registered nurses holding a Master's degree or higher, employed full time by UMC
- pharmacists holding a Doctoral degree in Pharmacy (PharmD), on staff or employed full time by UMC
- Physician Assistant's (PA's) and Advanced Practice Nurses (APN's) on staff or employed full time at UMC may conduct research as a Principal Investigator within the realm of their clinical specialty and research abilities as long as they possess the qualifications as stated in the IRB Policy & Procedure manual.

All Principal Investigators must meet the following qualifications in order to conduct research involving human subjects:

- have an active license in Nevada.
- be an active staff member in good standing at UMC.
- be familiar with the medical literature related to the drug/device/procedure/disease stated to be studied.
- be familiar with the protocol guiding the drug/device/procedure to be studied.
- have knowledge of known clinical and/or pharmacological potential of the investigational drug, device or procedure under study.
- have previous documented research experience as described in the IRB Policy & Procedure Manual and complete the CITI Course.

The IRB recognizes one Principal Investigator (PI) for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the Principal Investigator must be modified to meet the investigator's skills or have one or more additional qualified person as Co-investigator(s). All investigators must provide a curriculum vitae and/or other documentation to show qualifications listed above.

Resident/Student Investigators
With the exception of exempt research, students may not serve as Principal Investigators. They must have a staff physician sponsor who fulfills the principal investigator eligibility criteria and who will serve as Principal Investigator on the study. Any investigator whose status is considered to be "in training" (i.e. students and medical residents) may not serve as a Principal Investigator but may serve as a co-investigator.

Research Team
The PI and other individuals, also known as key personnel, who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol. All research team members must submit a copy of their CV and must have an active required UMC CITI Course Certification, or equivalent certifications

Ceding IRB oversight to another IRB
In some cases, the UMC IRB may agree to rely on another institution's IRB for oversight of a project. The Director, Clinical Research and Compliance or designee determines whether ceding/deferring IRB review is appropriate on a case-by-case basis. The Director/designee may seek consultation from the IRB Chair(s), UMC Administration, UMC Counsel, or others, when needed to make this determination. In general, however, ceding IRB review is allowable in situations including, but not limited to, the following:

- The Principal Investigator for the project is eligible to serve as principal investigator, without supervisory oversight,
- The expertise of the proposed IRB of record is equally or more appropriate to assess the research plans compared to UMC's IRB;
- There are no extenuating circumstances such that ceding review places UMC or the reviewing institution at compliance risk, or requires releasing confidential information about UMC personnel (e.g., history of noncompliance by study personnel).

When the UMC IRB will not consider relying on a non-UMC IRB for oversight

These decisions are also made on a case-by-case basis. In general, relying on a non-UMC IRB to provide oversight is generally not allowable in the following situations:

- The proposed IRB of record does not have an established or current Federalwide Assurance.
- The proposed IRB of record does not have sufficient knowledge of local context (as required by federal guidelines) to assume IRB oversight for sites that fall under UMC purview;
- An UMC study team member has a conflict of interest that requires a management plan and the management plan prohibits or limits activities that the individual can engage in related to human subjects research;
- The study likely qualifies for exemption (ceding review is not required for exempt research); and/or
- Studies for which federal regulations, or administrative or hospital policies otherwise prohibit or limit options for IRB reliance.

When it has been determined that the UMC IRB will rely on another IRB for oversight, in accordance with 45 CFR 46.102, the reliance on the outside IRB will be documented.

Note: UMC reserves the right to elect not to cede IRB review of an otherwise eligible study to another IRB if previous experience with that IRB indicates the reliance process will be protracted or if concerns arise during the reliance process (e.g., extensive negotiation regarding the IAA are required, the proposed IRB of record does not respond to queries, concerns about the human subjects' protection or regulatory compliance of the proposed IRB are noted, etc.).

31. REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

Investigators must promptly report to the Chairman of the IRB, in writing, any of the following occurrences:

- Any proposed changes in the approved research, including but not limited to:
  - Accrual closure
  - Accrual suspension
  - Changes in Principal Investigator, Co-Investigators, Research Staff
  - Addendums
  - Amendments
  - Study closure
  - Investigator Brochure changes
  - Modifications
  - Changes in Protocol
  - Revisions
  - Updates
  - Outcomes of monitor and site visits (including any deficiencies discovered)
    (Such changes may not be implemented without IRB approval except where necessary to eliminate apparent immediate hazards to human subjects.)
- Any proposed changes in a previously approved consent form (such changes may not be implemented without IRB approval.)
- Any deviation from the investigation plan.
  - *Reportable protocol deviations are deviations that are considered substantive and adversely affecting one of the following:*
    - *Rights or welfare of subjects*
    - *Safety of subjects*
    - *Willingness of subjects to continue with study participation*
    - *Integrity of the research data*
  - *If a protocol deviation is not considered substantive and/or affecting any of the above-mentioned areas by the PI, the protocol deviation is minor and doesn't need to be reported to the UMC IRB. If a protocol deviation is assessed as not reportable, it is not reportable at any time, not even at continuing review (Refer to UMC IRB Reporting Guidance for Protocol Deviations)*
- Use of an investigational drug or device without obtaining informed consent. (*This must be reported to the IRB within three days of the occurrence.)*
- Any unanticipated problems involving risks to human subjects or others, including data breaches. *(Data breaches must be reported to UMC's Privacy Officer immediately upon discovery. Investigators should expect to pay all costs incurred by UMC that result from a breach of data in the investigator's custody. Such costs may include notifications and other mitigations that are determined to be necessary to reduce the harm to the subjects of the breach.)*
- Any unanticipated adverse effects occurring during an investigation, including but not limited to:
  - Unexpected adverse events that are related to research
  - Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm
  - Other unanticipated information that indicates participants or others might be at increased risk of harm
  - Information that indicates a change to the risks or potential benefits of research
  - A breach of confidentiality
  - Change in FDA (or equivalent regulatory body) labeling or withdrawal from marketing of a drug, device, or biologic used in research protocol.

- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Event that requires prompt reporting to the sponsor;
- Sponsor imposed suspension for risk;
- New information that may affect adversely the safety of the participants or the conduct of the clinical trial
- Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.

(*These must be reported to the IRB within five days of being made aware of the occurrence.)*

- Any death or serious injury to a participant in a study, which is or may be in any way related to the study. This must be reported to the IRB within five days of the occurrence.

Failure to comply may result in suspension or termination of the protocol. An investigator will cooperate fully with the IRB and provide any requested information on any aspect of research of an investigation.

32. NONCOMPLIANCE REPORTING

All members of UMC involved in human subject research are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and state regulations and institutional and IRB policies governing the conduct of research involving human subjects.

The Chairs of the IRBs and the Director will promptly handle (or direct staff to handle), and, if necessary, investigate all complaints, concerns, appeals, and reports resulting from not-for-cause or a directed for cause reviews received by the IRB. This includes complaints, concerns, and appeals from investigators, research subjects and others. In order to comply with 45 CFR 46.103 and 21 CFR 56.108, UMC will promptly report to the Office of the Human Research Protection (OHRP) and US Food and Drug Administration (FDA) the necessary information that describes events affecting human research participant safety. The required reporting events include any serious or continuing non-compliance with federal policy or determinations made by the IRB.

Definitions

Non-compliance:	Failure to follow the regulations; institutional policies governing human subject research; or requirements or determinations of the IRB. This may pertain to the principal investigator, the investigator's research staff, or any member of the human research protection program including the IRB and the IRB administrative staff.
Minor or sporadic Non-compliance:	Failure to comply with IRB policies, which in the opinion of the IRB Chair and Director (or designee) is administrative in nature. Examples of minor or sporadic non-compliance could include turning in a report of an unanticipated problem a day late or failure to date a consent form.
Serious Non-compliance:	Failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB and which, in the judgment of either the IRB Chair or the convened IRB, increases risks to subjects, decreases potential benefits, adversely affects the rights, welfare, and safety of the research subjects, or jeopardizes the integrity of the human research protection program. Research being conducted without prior IRB approval is considered serious noncompliance.

Continuing Non-compliance:	Suggests a likelihood that instances of non-compliance will continue without intervention. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.
Allegations of Non-compliance:	An unproved assertion of non-compliance.
Finding of Non-compliance:	An allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator of that the protocol was willfully not followed would represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance.)

Receipt of Allegations of Non-compliance
Reports of non-compliance may be provided to the IRB Chair, IRB members, and IRB staff from anyone inside or outside of UMC who has reason to believe that the non-compliance has occurred. Investigators and research staff are required to report any observed, suspected, or apparent non-compliance to the IRB within five (5) calendar days of discovering it. This refers to all non-compliance as previously described up above. These complaints will be accepted in writing only. Reports of non-compliance must contain enough information to assess whether the report is sufficiently credible so that potential evidence of noncompliance may be identified and acted upon.

Review of Allegations of Non-compliance
Immediately upon receipt of an allegation of serious non-compliance by an investigator, the Director or designee will forward the allegation and investigation report to the IRB chairman, or designee, and the IRB committee.

All allegations of non-compliance will be reviewed by the IRB Chair and Director. They will review:

- All documents relevant to the allegation;
- The last approval letter from the IRB;
- The last approved version of the IRB protocol application;
- The last approved consent document;
- The last approved Investigator's Brochure, if applicable;
- The grant, if applicable; and
- Any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

The IRB Chair and Director will review the allegation and make a determination as to the truthfulness of the allegation. They may request additional information or an audit of the research in question.

If in the judgment of the IRB Chair and Director, the reported allegation of non-compliance is not true, no further action will be taken. If in the judgment of the IRB Chair and Director, the reported allegation of non-compliance is true, the non-compliance will be processed as outlined below in this policy.

If in the judgment of the IRB Chair and Director, any allegation or findings of non-compliance warrants suspension or termination of the research before completion of any review or investigation to ensure protection of the rights and welfare of subjects, the IRB Chair may terminate or suspend the research as described in below with subsequent review by the convened IRB.

Review of Findings of Non-compliance
If in the judgment of the IRB Chair and Director, the reported finding of non-compliance is not serious, not continuing, and the proposed corrective action plan seems adequate, no further action is required and the IRB is informed at the next

convened meeting. Otherwise, the matter will be presented to the IRB at a convened meeting with a recommendation that a formal inquiry (described below) will be held.
All findings of non-compliance referred to the IRB will be reviewed at a convened meeting. All IRB members will receive:

- All documents relevant to the allegation;
- The last approval letter from the IRB;
- The last approved IRB protocol application; and
- The last approved consent document.
- At this stage, the IRB may:
- Find that there is no issue of non-compliance;
- Find that there is noncompliance that is neither serious nor continuing and an adequate corrective action plan is in place;
- Find that there may be serious or continuing non-compliance and direct that a formal audit (described below) be held; or
- Request additional information.

Audit Procedures
A determination may be made by the IRB that an audit is necessary based on several issues that may include but are not limited to:

- Subjects' complaint(s) that rights were violated;
- Report(s) that investigator is not following the protocol as approved by the IRB;
- Unusual and/or unexplained adverse events in a study;
- FDA/sponsor audit report of an investigator;
- Repeated failure of investigator to report required information to the IRB.

A subcommittee is appointed consisting of IRB members, and non-members if appropriate, to ensure fairness and expertise. The subcommittee is given a charge by the IRB, which can include any or all of the following:

- Review of protocol(s) in question;
- Review of FDA/sponsor audit report of the investigator, if appropriate;
- Review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the investigator's execution of her/his study involving human subjects;
- Interview of appropriate personnel if necessary;
- Preparation of either a written or oral report of the findings, which is presented to the full board at its next meeting;
- Recommend actions if appropriate.

Final Review
The results of the audit will be reviewed at a convened IRB meeting where the IRB will receive a report from the subcommittee. If the results of the audit substantiate the finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

- Request a correction action plan from the investigator;
- Verification that subject selection is appropriate and observation of the actual informed consent;
- An increase in data and safety monitoring of the research activity;
- Request a directed audit of targeted areas of concern;
- Request a status report after each subject receives intervention;
- Modify the continuing review cycle;
- Request additional Investigator and staff education;
- Notify current subjects, if the information about the non-compliance might affect their willingness to continue

participation;
- Direct that no new subjects be added to any ongoing studies;
- Suspend the study (See below); or
- Terminate the study (See below).

The investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described in the reporting requirements.

Additional Actions
A finding of serious or continuing non-compliance may also result in the following sanctions, among others:

- Suspension or termination of IRB approval of specific research protocols or of all research involving human subjects in which the investigator participates.
- Sponsor actions. In making decisions about supporting or approving applications or proposals covered by this policy the Department of Health and Human Services or Agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension as described above, and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the Department of Health and Human Services or Agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects.
- Institutional or individual action by the federal OHRP and/or the FDA. The federal OHRP and/or the FDA may
    - withhold approval of all new UMC studies by the IRB;
    - direct that no new subjects be added to any ongoing studies;
    - terminate all ongoing studies, except when doing so would endanger the subjects; and or
    - notify relevant state, federal and other interested parties of the violations.
- Individual disciplinary action of the investigator or other personnel involved in a study, up to and including dismissal, pursuant to UMC policies and procedures.
- Notification of current participants when such information may relate to participants' willingness to continue to take part in the research

Failure to secure necessary IRB approval before commencing human subject research must be reported to the chief of staff, chief executive officer, and chief medical officer for disciplinary action.

Reporting
Serious or continuing noncompliance with regulations or the requirements or determinations of the IRB; and suspensions or terminations of IRB approval will be reported to the appropriate regulatory agencies such as the FDA, OHRP, and institutional officials, according to the non-compliance procedures.

Conduct of Quality Assurance/Quality Improvement Activities for IRB Operation
The Quality Assurance methods whereby the IRB processes are reviewed and tracked internally are described in the UMC HRPP Quality Assurance / Quality Improvement Plan. The IRB staff will conduct investigations and audits of ongoing research when the IRB directs an audit be conducted or a complaint or allegation of non-compliance is received. In addition, the staff will conduct "for cause" and "not for cause" audits of research.

If the IRB determines that an investigator has committed a serious or continuing non-compliance with the requirements of the IRB, such action by the investigator will be reported to the hospital administration, the appropriate medical staff department chairperson, and the appropriate governmental department or agency head.

33. SUSPENSION OR TERMINATION OF AN IRB APPROVAL

Definitions

Suspension	An action taken by the IRB that temporarily or permanently halts some or all research procedures short of a termination until the IRB determines whether the research may recommence, with or without modifications, or be terminated.
Termination	An action taken by the IRB that ends a study where no further contact with human subjects or their individually identifiable information is planned; no subjects are or will be treated or followed; no future data is gathered and analyzed; and any final reports or publications are complete.

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with regulatory requirements, the IRB's requirements, or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, hospital administration, appropriate medical staff department chairperson, and the appropriate government department or agency head.

In light of the number of IRB members, diversity of membership, range of expertise of members, its staff of consultants and dedication of the members for the protection of the rights of human subjects, there will be no appeal of the decisions of this IRB.

In the event that a study approval is suspended or terminated, the IRB or person ordering the termination and suspension will:

- Consider actions to protect the rights and welfare of currently enrolled participants;
- Consider whether procedures for withdrawal of enrolled subjects address their rights and welfare;
- Consider informing current participants of the termination or suspension;
- Report suspensions and terminations of IRB approval to FDA and appropriate organizational officials within 30 days.

34. PREPARATION & RETENTION OF RECORDS

The IRB, with the assistance of the designated IRB Coordinator, will prepare and maintain adequate documentation of the IRB's activities including, copies of all items reviewed, including, but not limited to research proposals, investigators' brochures and recruitment materials; scientific evaluations (if applicable) that accompany the proposals; approved consent documents; approved HIPAA Authorizations document, if separate from the informed consent form, any proposed modifications and the IRB action on each modification; progress reports submitted by investigators; reports of injuries to subjects and serious adverse events; documentation of protocol violations; documentation of non-compliance with applicable regulations; approved sample consent documents; continuing review activities; copies of all correspondence between the IRB and investigators; and statements of significant new findings provided to subjects and, when reviewed, must be documented in the minutes.

A copy of the approved consent form will be returned to the investigator with the date of IRB approval noted on each page and a copy of the approved consent form will be retained in the IRB record.

The IRB records include:

1. Protocols;
2. Scientific Evaluations;
3. Progress reports submitted by investigators;

4. Reports of injuries to participants;
5. Records of continuing review activities;
6. Correspondence between IRB and investigators;
7. Statements of significant new findings provided to participants
8. For initial and continuing review of research by the expedited procedure:
    a. The specific permissible category
    b. Description of action taken by reviewer
    c. Any findings required under the regulations
    d. Documented rationale for approval of more than minimal risk
    e. For exemption determinations the specific category of exemption.
9. Unless documented in the IRB minutes, determinations required by the regulations and protocol-specific findings supporting those determinations for
    a. Research involving pregnant women, fetuses, and neonates.
    b. Research involving prisoners
    c. Research involving children
10. For each protocols initial and continuing review, the frequency for the next continuing reviews.

IRB record retention guidelines:

1. IRB records relating to research are retained for at least three (3) years after completion of the research.
2. IRB records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.
3. If a protocol is cancelled without subject enrollment, IRB records are maintained for at least three (3) years after cancellation.
4. Records are kept in the IRB office in chronological order from the start date of the research.

Proceedings of the IRB minutes must be written and available for review by the next regularly scheduled IRB meeting date. Once the minutes are approved by the IRB Chairman or Vice Chairman at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority. The IRB minutes must contain sufficient detail to show:

1. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area;
2. Attendance at the meetings
3. When an alternate member, replaces a primary member
4. Actions taken by the IRB including those involving full review. The IRB must use the minutes to notify IRB members of actions taken through expedited review and those studies that have been determined to be exempt from IRB review;
5. Separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB;
6. Documentation that the research meets the four required criteria [45 CFR 46.116(d)] when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent;
7. Documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived;
8. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms.
9. For initial and continuing review, the approval period.
10. The vote on actions, including the number of members voting for, against, and abstaining;
11. A note indicating that when an IRB member has a real or potential conflict of interest, as defined by the section entitled "Conflict of Interest" in this policy, relative to the proposal under consideration, what the conflict of interest generally involves, that the IRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained);

12. The basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs;
13. A written summary of the discussion of controversial issues and their resolution;
14. Review of additional safeguards to protect vulnerable populations if entered as study subjects when this is not otherwise documented in IRB records, and documentation of the required IRB findings in order to approve research involving persons with impaired decision-making capacity (see Section 10.4.2);
15. The rationale and determination of the level of risk, if not recorded elsewhere in IRB records;
16. The frequency of continuing review of each proposal, as determined by the IRB, if not recorded elsewhere in IRB records;
17. The eligibility category for each expedited review of new proposals;
18. Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization;
19. Key information provided by consultants (if applicable) will be documented in the minutes or in a report provided by a consultant;
20. Documentation of the approval period for initial and continuing review;
21. Signature of IRB Chair or Vice-Chair and IRB Coordinator certifying IRB-approved minutes.

A copy of the IRB-approved minutes for each IRB meeting must be sent to the Medical Executive Committee who will then forward to the Hospital Board of Trustees

The formal letter of approval will not be sent to the investigator until all changes and documents requested by the IRB have been received. A list of IRB members identified by name, earned degrees, representative capacity, and indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contribution to IRB deliberations. Any employment or other relationship between each member and the institution and any investigator or sponsor of any investigational study reviewed and monitored by the IRB will be described in the records; for example, full-time employee, part-time employee, a member of a governing panel or board, stockholder, paid or unpaid consultant.

Written procedures for the IRB as required by 21 CFR56.108(a) and (b).

Statements of significant new findings provided to subjects, as required by 21 CFR 50.25.

Per 45 CFR 46.115(b), The records required by USFDA regulations will be retained for at least three years after completion of the research, and the records will be accessible for inspection and copying by authorized representatives of the USFDA at reasonable times and in a reasonable manner.

Minutes will be forwarded for review to the Medical Executive Committee and, in turn, to the Board of Hospital Trustees of University Medical Center.

35. EDUCATION FOR MEMBERS, ADMINISTRATORS, PI'S, CRC'S/ASSISTANTS

One of the roles of the UMC IRB is to provide educational opportunities to assist all investigators and members of their research team, as well as, IRB Members and affiliated personnel with education specific to IRB. The educational purpose is to focus on topics, regulations and guidelines that are most pertinent to research relating to biomedical, drug, device, behavioral science, and clinical procedures to ensure awareness of the fundamental requirements, responsibilities and ethical and regulatory issues related to the conduct of human subject research by the above-noted categories of personnel.

The UMC IRB requires that investigators and their research team have either documented research experience on their CV, have completed the CITI course or have attended an IRB educational seminar and able to provide a certificate of completion.

The UMC IRB maintains a subscription to the web-based "CITI: The Protection of Human Research Subjects" sponsored by the Collaborative IRB Training Initiative (CITI) and the University of Miami.

To satisfy the education requirement, investigators and members of their research team must complete and pass one of the following series of CITI modules:

- Biomedical Research Group (Human Subjects Protections (HSP) module), and /or
- Social/Behavioral Research Group

All investigators and their research staff conducting studies at UMC that fall under the criteria for IRB review must complete one of the educational requirements documented above. The CITI Certification is only valid for three (3) years and the study team is required to have active certification for the duration of the study. A refresher course for these required modules is available and must be completed prior to the expiration of the initial certification.

ELEMENTS

1. UMC will provide educational opportunities for the above-noted personnel annually.
   a. Opportunities will include self-test training manuals, IRB-specific local conferences, and opportunities to attend national conferences, and information on educational opportunities over the Internet. Most educational opportunities include CME's, CEU's, or certificates of completion.
   b. Documentation of education will be monitored and filed in the IRB Office.
2. New Principal Investigators:
   a. New Principal Investigators, Sub or Co-Investigators' who cannot demonstrate previous peer reviewed research activity within the last five (5) years will be asked to complete the CITI: Human Subjects Research Protection Course (available on-line). The CITI: Human Subjects Research Protection Course is also available to the Principal Investigators' Sub or Co-Investigators and research coordinators and assistants.
3. Current Principal Investigators:
   a. Because many federally funded agencies that sponsor research protocols require documented continuing education in research, it is highly recommended that IRB Members, Hospital Administrators, Principal Investigators, and Clinical Research Coordinators/Assistants complete at least one (1) educational opportunity annually.

36. VENDOR VISITATION POLICY

All investigational drug, device and procedure studies are under the auspices of the IRB and must have a Principal Investigator who is a member of the UMC Medical and Dental Staff and who will submit the application for review/comment/recommendation to the Medical Staff Department/IRB Coordinator and who will assume responsibility for ensuring the packet is complete and accurate for approval consideration by the Institutional Review Board (IRB) at University Medical Center (UMC).

Investigational drugs, devices, and procedures will be used only under the direct supervision of the Principal Investigator or Co-investigator who will be a member of the Active, Associate or Provisional staff category of the Medical Staff of University Medical Center. A Principal or Co-investigator may not exceed privileges approved on their individual Delineation of Privileges Forms.