Midwest Division

Institutional Review Board

POLICIES AND STANDARD OPERATING PROCEDURES

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I. INTRODUCTION

Current federal regulations require that all Institutional Review Boards (IRBs) have written policies and procedures, and that activities at the institution are carried out as described in those written policies and procedures. Standard Operating Procedures (SOPs) are written to enable IRBs to maintain a system of compliance. The SOPs of an IRB reflect not only the laws and regulations, but also the underlying ethical principles that are the basis of the IRB's mandate, and reflect the overarching commitment of the institution to protect the human subjects involved in research conducted within its jurisdiction.

The SOPs contained in this document apply to the daily operations of the HCA Midwest Division IRB. They apply to all research in which HCA Midwest Division is the applicant organization, or is otherwise engaged in research. The SOPs also apply to research conducted by affiliated physicians, in which the institution is not directly engaged in the research.

The forms, checklists, and other documents in these SOPs are included in order to assure that the procedures are integrated into the daily activities of not only IRB members and staff, but into the activities of the investigative site as well. The forms are flexible and take into account numerous details of the day-to-day activities required by the IRB to fulfill its mandate.

These SOPs should be reviewed periodically to ensure that they are up-to-date, that new legislation or regulations are reflected in the policies and that daily activities are being performed as described in the SOPs.

These policies are based on current state and federal regulations, ethical principles, and guidelines for the protection of human subjects involved in biomedical and behavioral research. The policies state what this institution requires for the ethical conduct of clinical research.

II. LIST OF ABBREVIATIONS

ADE	Adverse Drug Event/Experience
AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CIM	Certified IRB Manager
CIP	Certified IRB Professional
CLIA	Clinical Laboratory Improvement Act
CSO	Consumer Safety Officer (FDA)
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organizations
DHHS	Department of Health and Human Services (or HHS)
DSMB	Data Safety and Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVD	In Vitro Diagnostic
NDA	New Drug Application
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities (NIH)
OHRP	Office for Human Research Protections
PI	Principal Investigator
PMA	Premarket Approval (Application)
QA	Quality Assurance
QI	Quality Improvement
RAC	Regulatory Affairs Certified
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

III. STATEMENT OF AUTHORITY AND PURPOSE

A. Governing Principles

Institutional Review Boards (IRBs) are guided by the ethical principles applied to all research involving humans as subjects, as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, titled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report"). These principles are defined in the Belmont Report (Appendix B) as follows:

- **Beneficence** – The sum of the benefits to the subject and the importance of the knowledge to be gained so outweigh the risks to the subjects as to warrant a decision to allow the subject to accept these risks.

- **Autonomy** – Legally effective informed consent is obtained, unless the requirements for waiver of informed consent are met by adequate and appropriate methods in accordance with the provisions of applicable regulations.

- **Justice** – The selection of subjects is equitable and is representative of the group that will benefit from the research.

B. Authority

1. An Institution's IRB is established and empowered by that Institution's executive authorities, and by the Institution's Assurance with OHRP. An institution may have more than one IRB, but all must subscribe to the same underlying principles and authorities. This Institution, HCA Midwest Division, requires that all research projects involving human subjects or living human material (tissues, cells, serum, etc) that are conducted at a HCA Midwest Division facility be reviewed and approved by the IRB prior to initiation of any research-related activities, including recruitment and screening activities.

2. Except for research in which the only involvement of humans is in one or more of the categories exempted or waived under 45 CFR 46 Section 101(b)(1-6) or 101(i), all research involving human subjects, and all other activities which even in part involve such research, are subject to these policies and procedures if one or more of the following apply:
   a. The research is sponsored (funded) in whole or in part by HCA Midwest Division, or the federal government;
   b. HCA Midwest Division is the applicant organization (or the contract organization has requested that a project be reviewed by HCA Midwest Division's IRB as a service to them);
   c. The research is conducted by or under the direction of any employee of HCA Midwest Division, in connection with his or her official responsibilities, or using any property or facility of HCA Midwest Division;
   d. The research involves the use of nonpublic information to identify or contact subjects;
   e. A physician or a medical professional staff of an HCA Midwest Division affiliated healthcare facility, which is engaged in a research project that utilizes the services of one or more of the institution's facilities.

3. The IRB has the authority to ensure that such research is designed and conducted in a manner that protects the rights and welfare of participating subjects. Specifically:
   a. The IRB may disapprove, modify or approve studies based upon consideration of human

subject protection aspects;

b. The IRB reviews, and has the authority to approve, require modification in, or disapprove, all research activities that fall within its jurisdiction;
c. The IRB has the authority to conduct continuing review as it deems necessary to protect the rights and welfare of research subjects, including requiring progress reports from the Principal investigators and auditing the conduct of the study, observing the informed consent process and/or auditing the progress of any study under its jurisdiction as it deems necessary to protect the rights and welfare of human subjects;
d. The IRB may suspend or terminate approval of a study; and
e. The IRB may place restrictions on a study.

4. Regarding federally funded research, if the study is part of an application to a federal sponsoring agency, the human protocol must be reviewed by the IRB when the application is processed, and prior to expenditure of any grant funds.

5. Research that has been reviewed and approved by the IRB may be subject to review and disapproval by institutional officials or other committees. However, those officials or committees may not approve research if it has been disapproved by the IRB.

C. Responsibility

1. IRB Review of Research

a. All applicable research involving human subjects (see above), and all other activities must be reviewed and approved by the IRB prior to implementation. No intervention or interaction with human subjects in research, including recruitment, may begin until the IRB has reviewed and approved the research protocol. Specific determinations as to the definition of "research" or "human subjects," and their implications for the jurisdiction of the IRB under Institutional policy will be determined by the Institution and the IRB.

b. The purpose and responsibility of the IRB is to protect the rights and welfare of human subjects. The IRB reviews and oversees such research to ensure that it meets well-established ethical principles and that it complies with federal regulations at 45 CFR 46 and 21 CFR 50 and 56, that pertain to human subject protection, as well as any other pertinent regulations and guidelines, such as the Good Clinical Practice (GCP) Guideline (E6) of the International Conference on Harmonization (ICH).

c. According to federal regulations, activities that require IRB review include any activities involving the collection of data through intervention or interaction with a living individual, or involving identifiable private information regarding a living individual. Specific activities that require IRB review include, but are not necessarily limited to the following:

(1) Any experiment that involves an investigational drug or device and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration (FDA) under relevant investigational drug or medical device provisions of the Food, Drug, and Cosmetic Act, or experiments that do not meet the requirements for prior submission to the FDA, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

(2) Collection of data about a series of standard procedures or treatments for dissemination or generalization.

(3) A patient's care or assignment to intervention is altered for research purposes in any way.

(4) A diagnostic procedure for research purposes that is added to a standard treatment.

(5) Systematic investigation involving innovative procedures of treatments, for example, if a physician plans to collect information about the innovation for scientific purposes or will repeat the innovation in other patients in order to compare it to standard treatment.

(6) Emergency use of an investigational drug or medical device. Note that when emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject, and data generated from such care *cannot be included in any report of a research activity*. (Except for 21 CFR 50.23)

(7) Human cell or tissue (genetic tissue) research that typically involves repositories that collect, store, and distribute human tissue materials for research purposes. However, human cell or tissue repositories activities *do not require* IRB review if material submitted to the repository satisfies *both* of the following conditions: (i) The material, in its entirety, was collected for purposes other than submission to the repository (*e.g.*, the material was collected solely for clinical purposes, or for legitimate but unrelated research purposes, with no "extra" material collected for submission to the repository); **and** (ii) The material is submitted to the repository without any identifiable private data or information, *i.e.*, no codes or links of any sort may be maintained, either by the submitter or by the repository, that would permit access to identifiable private data or information about the living individual from whom the material was obtained.

(8) Principal investigator-initiated research, where a Principal investigator both initiates and conducts, alone or with others, a clinical trial. In the case of Principal investigator-initiated studies, it is the Principal investigator's responsibility to keep the IRB informed of unanticipated non-serious research related events and unanticipated serious adverse events and other unexpected findings that affect the risk/benefit assessment of the research, even if the event occurred at a location for which the IRB is not the IRB of record. The IRB further recommends that an independent data safety monitoring board (DSMB) review all reportable adverse events, and that the DSMB reports are forwarded to the IRB in addition to individual reports.

(9) Case studies, such as when a series of subject observations are compiled in such a way as to allow possible extrapolation or generalization of the results from the reported cases. Such activity constitutes research that must be reviewed by the IRB. Additionally, this type of activity must always be reviewed by the IRB when there is intent to publish or disseminate the data or findings.

2. Failure to Submit a Project for IRB Review

The consequences of engaging in activities that qualify as research subject to IRB review, without obtaining such review, are significant. To do so is in violation of Institutional policy. Results from such studies may not be eligible for publishing unless IRB and other applicable institutional approval have been obtained prior to collecting the data. If a Principal investigator begins a project and later finds that the data gathered could contribute to the existing knowledge base, or

that he or she may wish to publish the results, the Principal investigator should submit a proposal to the IRB for review as soon as possible. If the IRB does not subsequently approve the research, data collected cannot be used as part of a thesis or dissertation, and/or the results of the research cannot be published. Furthermore, FDA may reject such data if it is submitted in support of a marketing application.

IV. GENERAL ADMINISTRATION

A. POLICIES AND PROCEDURES MAINTENANCE

1. Policy

HCA Midwest Division's IRB recognizes that Standard Operating Procedures (SOPs) provide the framework for the ethical and scientifically sound conduct of human research, and that adherence to established SOPs helps to ensure high quality and integrity of the review process, regardless of changes in personnel. The IRB hereby establishes the procedures for development and maintenance of SOPs covering IRB operations.

2. Review, Revision, Approval of Policies and Procedures

a. Changes to regulations, federal guidelines, or research practices as well as the policies and procedures of the IRB or HCA Midwest Division may require a new SOP or policy, or a revision to a previously issued SOP or policy.

b. New or revised policies will be reviewed and approved by the IRB Administrator, with input from the IRB Staff and HCA Midwest Division's Medical Director.

3. Policy Dissemination and Training

a. When new or revised policies are approved, they will be disseminated to the appropriate individuals & departments.

b. Training will be provided to all IRB members and staff on any new or revised policy.

c. Each new IRB member or staff employee must review all applicable SOPs and policies prior to undertaking any responsibilities at the IRB.

4. Responsibility

a. The Institutional Official (HCA Midwest Division's Legal Counsel) is responsible for granting final approval (as appropriate) to new and revised IRB policies.

b. The IRB Department is responsible for developing and periodically reviewing and modifying (as appropriate) IRB standard operating policies and procedures.

c. IRB members and staff are responsible for reviewing IRB standard operating policies and procedures, and providing feedback upon their content. IRB members and staff may also participate in the development of new policies as needed to reflect IRB operations.

5. Applicable Regulations And Guidelines

21 CFR 56.108, 56.109, 56.113
45 CFR 46.108

B. TRAINING AND EDUCATION

1. Policy

Training of staff and members is critical if the IRB is to fulfill its mandate to protect the rights and welfare of research subjects in a consistent manner throughout the HCA Midwest Division research community. IRB members, staff, Principal investigators, and others charged with responsibility for reviewing, approving, and overseeing human subject research should receive detailed training in the regulations, guidelines, ethics and policies applicable to human subject's research.

2. Training

a. IRB staff and members who oversee research on human subjects, as defined in 45 CFR 46.102 (f) and/or 21 CFR 56.102(e), will receive initial and ongoing training regarding the responsible review and oversight of research. The following examples are subjects that should be included in the training:

1. Ensuring that informed consent be obtained prior to implementing a protocol;
2. Complying with institutional policies and regulatory agencies' policies during implementation of research;
3. Providing for the safety and well-being of the patient enrolled in a protocol (research subject) during all research activities;
4. in an FDA-regulated study, complying with Form 1572, Statement of Investigator, that must be provided to the study sponsor prior to beginning a Phase 1, 2 or 3 study OR the written agreement with the sponsor for device studies; and
5. reporting immediately to the IRB any deviations from the protocol or situations that may qualify as scientific or research misconduct.

b. HCA Midwest Division Principal investigators who conduct human subject's research and researchers who come into contact with human subjects will receive initial and ongoing training regarding the protection of human subjects.

c. The IRB Administrator establishes the educational and training requirements for members and staff, and researchers. Initial and ongoing training is provided and documented in each individual's' administrative file.

d. Members of the IRB will also be provided continuing training in areas germane to their area of review responsibilities.

e. IRB staff will receive initial and continuing training in the areas of their administrative responsibilities, including all Standard Operating Procedures (SOP) and Policies.

f. IRB members and staff, and researchers will be encouraged to attend workshops and other educational opportunities focused on IRB functions. HCA Midwest Division will support such activities to the extent possible and as appropriate to the responsibilities of members and staff.

3. Documentation

Training and continuing education shall be documented and added to the records of the IRB as described in these SOPs.

4. Research Misconduct: **i**s defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Fabrication is making up data or results and recording or reporting them; falsification is manipulating research materials, changing or omitting data or results such that research is not accurately reflected in the research record; plagiarism is the use of another's work product without giving appropriate credit. ---A Guide to the Handling of Scientific Misconduct Allegations at the NIH, http://www1.od.nih.gov/oir/sourcebook/ResEthicsCases/NIH%20Misconduct2.pdf

4. Responsibility

The IRB Administrator is responsible for establishing, conducting and/or supervising all relevant training programs for IRB members and staff.

5. Applicable Regulations And Guidelines

21 CFR 56.107
45 CFR 46.107
OHRP IRB Guidebook
NIH NOTICE: OD-00-039 Required Education in the Protection of Human Research Participants

C. MANAGEMENT OF IRB PERSONNEL

1. Policy

Competent staff functions to provide consistency, expertise, and administrative support to the IRB, and serve as a daily link between the IRB and the research community. Thus, the IRB staff is a vital component in the effective operation of HCA Midwest Division's human subject's protection program. A high level of professionalism and integrity is expected.

2. Job Descriptions and Performance Evaluations

Members of the IRB staff should have a description of the responsibilities expected of their positions. The performance of IRB staff will be reviewed according to current HCA Midwest Division policy.

3. Staff Positions

Staffing levels and function allocation will be determined according to policy, management assessment of support requirements, and budget constraints.

4. Hiring and Terminating IRB Staff

The human resource policies of HCA Midwest Division determine the policies for recruiting and hiring staff.

5. Documentation

The policies of HCA Midwest Division determine the means of identifying, documenting and retaining formal staff interactions (such as performance reviews).

6. IRB Administrator Functions

The IRB Administrator is instrumental in ensuring that the IRB meets their primary responsibility of protecting the rights and welfare of human research subjects by:

a. Ensuring that submitted research is reviewed efficiently and consistent with federal regulations by:
   (1) Having thorough knowledge of and ability to apply HHS/FDA federal regulations.
   (2) Assuming responsibility for the education of IRB members and staff regarding the conduct of research.
   (3) Helping the IRB Chairperson to determine which studies are eligible for expedited review, or qualify for exemption from continuing IRB oversight.
   (4) Providing a pre-review of submitted materials, to help the Principal investigators address human subject's protections issue before they are brought to the IRB.
   (5) Conducting site visits as appropriate.
   (6) Effectively communicating with Principal investigators, sponsors, and IRB members.
   (7) Obtaining and distributing information required for Chairperson or IRB review
   (8) Providing data entry to computer tracking system, generating letters, creating files and mailing notices to Principal investigators.
   (9) Maintaining, filing, and archiving systems that allow access to open and closed studies.

b. Maintaining accurate records of IRB actions by:
   (1) Periodically reviewing IRB policies and procedures to ensure appropriate functioning of the IRB.
   (2) Preparing Agendas for IRB meetings.
   (3) Preparing Minutes for IRB meetings.
   (4) Preparing and sending timely letters to the Principal investigators, informing them of the IRB's review of their study.
   (5) Documenting communications with sponsors, Principal investigators, regulatory entities, and any others involved in the conduct of submitted research.
   (6) Maintaining an accurate and comprehensive database of reviewed and approved research.
   (7) Maintaining records of expedited reviews, risk determinations, and any other activities that result in a review or action by IRB members.

c. Maintaining accurate files, both paper and electronic.

d. Ensuring that Principal investigators and Sponsors are informed of the actions and findings of the IRB by:
   (1) Reviewing IRB SOPs on a regular basis to ensure accurate information and disseminating

changes to Principal investigators, IRB members and staff.
(2) Providing direction and consultation to Principal investigators regarding current issues and ethical concerns associated with the implementation of regulations, policies, and procedures.
(3) Assuming content responsibility for the IRB website.
(4) Notifying Principal investigators and other appropriate entities of IRB actions.

e. Ensuring that the Institutional Official is informed of the actions and findings of the IRB by providing him/her with the IRB minutes of each meeting, after they have been approved by the IRB Chairperson.

f. Ensuring that continuing review of approved research is conducted appropriately and in a timely manner by:
(1) Making Principal investigators aware of due dates for submission of renewal and other reports.
(2) Ensuring that information submitted by Principal investigators is adequate for effective review.
(3) Entering SAE reports into database and preparing a report for each IRB meeting.
(4) Entering external, off-site SAE reports into database, and preparing a quarterly report for the IRB.

g. Serving as IRB Interface for subjects, Principal investigators, sponsors and regulatory agencies by:
(1) Answering questions and supplying information when requested, and conveying IRB actions to appropriate individuals.
(2) Screening subject inquiries and resolving issues when possible, and conveying results of interactions with subjects to Principal investigators, sponsors, and IRB members as directed.
(3) Serving as the IRB liaison during audits by regulator entities or sponsors.

h. Overseeing adequacy of IRB membership by:
(1) Providing support to the Institutional Official in the recruitment or IRB members.
(2) Providing training and continuing education of IRB members.
(3) Maintaining IRB membership logs and coordinating submissions to regulatory agencies.
(4) Ensuring that a quorum is present, maintained, and documented during convened meetings.
(5) Keeping members apprised of their responsibilities regarding conflicts of interest.

i. Supporting the daily operations of the IRB.
j. The IRB Administrator is a voting member of the IRB and her attendance is considered in the count for a quorum. The IRB Administrator is authorized to implement expedited reviews under the following criteria:

1. Research activities that present no ;more than minimal risk
2. “minor changes“in previously approved research during the period (of one year or less) for which approval is granted.

Examples of minor changes to the Informed Consent that can be expedited:

1. Typographical errors
2. Reformatted page numbers
3. Changes in font
4. Additional verbiage to some sections that is standard language required and/or suggested by the IRB
5. Deletions and additions that are specifically delineated by the IRB
6. Changes in margins or sizes of tables
7. Change in contact information for the PIs or for emergency contacts
8. Ensuring that the informed consent is on letterhead
9. Addition or deletion of associates or staff
10. The reduction in the number of research participants
11. The deletion of questions in a survey"

7. IRB Supervisor Functions

The IRB Program Director, the Midwest Division Vice President of Quality and Risk Management, is instrumental in ensuring that the IRB meets their primary responsibility of protecting the rights and welfare of human research subjects by:

a. Overseeing the maintenance of accurate records of IRB actions by:

(1) Reviewing and suggesting modifications in IRB agendas and minutes prepared by the IRB Administrator.

(2) Periodically reviewing IRB policies and procedures to ensure appropriate functioning of the IRB.

b. Fulfilling reporting requirements to OHRP and other federal agencies, when appropriate.

c. Oversee performance of the IRB Administrator.

8. IRB Chairperson Functions

The IRB Chairperson:

a. Directs the full-committee meetings,
b. Performs Expedited Reviews, with the aid of the IRB Administrator, or delegates the review to appropriate IRB members,
c. And determines whether protocols are exempt from IRB review, with the aid of the IRB Administrator.

9. Applicable Regulations And Guidelines

IRB staff performance standards, management guidelines, and expectations will be established according to HCA Midwest Division policy.

D. CONFLICT OF INTEREST

1. Policy

a. In the research environment, openness and honesty are characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts of interest (COIs) should be eliminated wherever possible, and effectively managed and disclosed when they cannot.

b. COIs may reduce the objectivity of research by affecting the design, conduct, or reporting of research, or the analysis and interpretation of data (see 42 CFR 50.601 Subpart F). If research is designed or conducted improperly, its value is limited. It is not ethical to involve human subjects in research that is of no, or very limited, value. COIs may also directly affect subject safety. For example, a Principal investigator with a COI may, even if unwittingly, color the consent discussion by minimizing the risks or overstating the benefits, or dismissing the value of alternative treatments. A Principal investigator's willingness to report adverse reactions possibly related to the study article may also be affected. Principal investigators with a COI may also improperly include or exclude subjects (Draft Interim Guidance, OHRP, 2.1).

2. Principal investigator Disclosure Requirement

a. Principal investigators must disclose any significant financial interest with a research sponsor, and any other significant financial interest that may reasonably appear to affect or be affected by the research to the Midwest Division Vice President of Quality and Risk Management. The Officer will then send the IRB a report of his/her assessment of the real or perceived COI, and a plan regarding any real COI.

b. Principal investigators should disclose any COI to the IRB at the time of the initial application for a research protocol review, its renewal, or whenever the status of the COI changes.

3. IRB Member Disclosure Requirement

a. No IRB member may participate in the initial or continuing review of any research project in which the member has a conflict of interest, except to provide information as requested. It is the responsibility of each member of the IRB to disclose any COI in a study submitted to the IRB, and recuse him or herself from deliberations and voting.

4. Employees

Institutional staff whose job status or compensation is affected by research that is reviewed by the IRB must recuse themselves from any meeting at which such a protocol is reviewed.

5. Definitions of a COI (21 CFR 54.2)

a. **Compensation** affected by the outcome of clinical studies means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the Principal investigator in the form of an equity interest in the Sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.

b. **Significant equity interest** in the sponsor of a covered study means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through

reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $25,000 during the time the Clinical Principal investigator is carrying out the study and for 1 year following completion of the study.

c. **Proprietary interest** in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

d. **Clinical Investigator** means only a listed or identified Principal investigator or Sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the Principal investigator.

e. **Covered clinical study** means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single Principal investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), and large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

f. **Significant payments** of other sorts means payments made by the Sponsor of a covered study to the Principal investigator or the institution to support activities of the Principal investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical Principal investigator is carrying out the study and for 1 year following the completion of the study.

g. **Applicant** means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

h. **Sponsor** of the covered clinical study means the party supporting a particular study at the time it was carried out.

6. Determining The Existence and Nature of a COI

The IRB should consider the following to evaluate whether any of the disclosed interests are COIs that might affect subject safety or research objectivity (Draft Interim Guidance, OHRP, 4.3):

a. Who is the sponsor?
b. Who designed the research?
c. Who will analyze the safety and efficacy data?
d. What are the financial relationships between the Principal investigators and the sponsor?
e. Is there any Principal investigator compensation that is affected by the study outcome?
f. Does the Principal investigator have any proprietary interests in the product including patents, trademarks, copyrights, and licensing agreements?
g. Does the Principal investigator have equity interest in the sponsor, whether the sponsor is a

publicly held company or non-publicly held company?

h. Does the Principal investigator receive significant payments of other sorts from the sponsor (e.g. grants, compensation in the form of equipment, retainers for ongoing consultation, and honoraria)? If so, what are the specific arrangements for payment? Does the payment go to the institution or to the Principal investigator?
i. What is the payment per participant?
j. Are there any other arrangements?
k. What is the size and nature of the interest (including the potential increase in the value of the interest as a result of a favorable outcome of the research) (see 21 CFR 54.5)?
l. What steps have been taken to minimize potential for harm to subject or research objectivity?
m. What is the design and purpose of the study? Are there multiple investigators, some or most of whom without disclosable interests? Is the study a blind study? Are endpoints objective? Is measurement of endpoints done by someone other than the Principal investigators with the disclosable financial interest (see 21 CFR 54.5)?

7. Eliminating, Managing, or Reducing COIs

a. COIs should be eliminated if possible. The IRB will review the Investigators' disclosures and the COI Officer's assessment of any real COI, taking particular note of the impact of the COI on research integrity and risks to research participants. For and IRB member whose role is limited only to voting on the study, the risk is eliminated by their removal from the room during deliberations and voting.

b. The IRB will make the final decision about the COI and may require the following:
   (1) Prohibition of the Principal investigators' participation in the research
   (2) Management of the COI through:
      - Disclosure to subjects in the consent form of the COI
      - Public disclosure in articles and presentations
      - Limiting the role of the Principal investigators
      - External oversight of the study

c. The IRB will not approve research until it is satisfied that COIs have been or will be eliminated, managed, or reduced (Draft Interim Guidance, OHRP, 2.2).

8. Disclosure to Subject in Consent Form

a. If the IRB believes that a COI cannot be eliminated, and that the COI could be considered material to a potential subject's decision-making process (i.e., when subject is assessing risks and benefits or the merits of the research itself), the Principal investigator must inform the subject in the consent process and the form of the existence and nature of the COI (Draft Interim Guidance, OHRP, 5.2). The consent process and form should also document how the COI is being managed, and what additional protections have been put in place.

b. Subject must be informed in easily understandable language.

c. Principal investigators should disclose to subjects only COIs, not other financial interests.

d. The dollar amount of the COI should not be disclosed to the subject.

9. Confidentiality of Financial Disclosure Statements

To the extent permitted by law, the IRB will maintain the confidentiality of all records of financial disclosure (see 42 CFR 50.606). For example, if any such records are sought under the Freedom of Information Act (FOIA), the custodian of the records will seek legal counsel and request that all applicable exemptions to disclosure under FOIA are asserted.

10. Education and Training in COI

IRB members and staff are encouraged to participate in available education and training activities related to financial conflict of interest issues including those required by the institution.

11. Responsibility

a. Questions regarding COI should be referred to the IRB Department.

b. IRB Administrator (or equivalent) is responsible for monitoring the COI status and disclosures of IRB members. The IRB will maintain records of financial disclosures and actions taken with respect to each COI for at least one year from the date of completion of research (see 42 CFR 50.604).

c. IRB Chairperson (or designee) is responsible for identifying COI disclosures before beginning every IRB meeting. At the beginning of the meeting, the IRB Chairperson will ask if any member has a COI regarding any protocol to be discussed at the meeting. If a member has a COI, s/he will recuse him/herself from the discussion and vote of the protocol.

d. The IRB may suspend research if they believe that an existing COI is not being reduced or managed in accordance with their directions, or a new COI is deemed to threaten the safety of the subject or the objectivity of the research, or upon discovery that the Principal investigator failed to disclose a COI.

12. Applicable Regulations And Guidelines

21 CFR 56.107(e)
21 CFR 54
42 CFR 601, 604
42 CFR 50, Subpart F
FDA Information Sheets, FAQs, Section II, question 12
Draft Interim Guidance: Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection, January 10 2001, OHRP, HHS

E. SIGNATORY AUTHORITY

1. Policy

The IRB Administrator is authorized to sign any and all documents in connection with the review and approval of research projects involving the use of humans as subjects, which have been reviewed and approved by the IRB pursuant to IRB policies and procedures, provided the Chairperson or designated reviewer grants this authority in writing or verbal permission.

In all cases, the IRB Administrator must sign the Chairperson's (or Designated Reviewer's) name along with the IRB Administrator's initials, to indicate that s/he signed for the Chairperson (or Designated Reviewer's).

2. Definitions

a. **Review and approval of research projects:** Any action or decision taken by the IRB through full or expedited review mechanisms, which grants or may appear to grant Principal investigators with initial or continuing approval of research involving human subjects.

b. **Routine correspondence:** Any action, letters, memos or emails between the IRB staff and members of the IRB and between IRB staff and Principal investigators that provides information concerning the review of research protocols by the IRB or staff which do not imply or appear to imply approval of research.

c. **Decisions made by Chairperson:** Any letters, memos or email sent representing the decision or opinions of the Chairperson of the IRB or their respective designee as long as such correspondence does not imply review and approval of research projects.

3. Authorization for Signatory Authority

Authorization to sign documents not described in this policy may be made in writing to the IRB Administrator.

4. Correspondence with External Agencies

The HCA Midwest Division Vice President of Quality and Risk Management or his/her designee will sign any letters or memos sent to agencies of the federal government, except for Prisoner Certification Letters, which will be sent directly from the IRB Administrator.

5. Responsibility

a. The Institutional Official is responsible for establishing the overall procedure for delegating signatory authority.

b. IRB Administrator (or equivalent) is responsible for documenting and implementing signatory authority delegations.

c. IRB Chairperson, members and staff are responsible for adhering to institutional signatory authority policies.

6. Applicable Regulations And Guidelines

45 CFR 46.103, 46.115

V. IRB ORGANIZATION

A. COMPOSITION OF THE IRB

1. Policy

a. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB should also be able to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

b. Therefore, the IRB shall consist of at least five regular, voting members. Qualified persons from multiple professions and of both genders shall be considered for membership. IRB membership shall not consist entirely of men or of women.

c. HCA Midwest Division will make every effort to have a diverse membership appointed to the IRB, with available expertise needed to conduct its functions.

2. Membership Selection Criteria

a. The members of the IRB shall be sufficiently qualified through experience and expertise to review research proposals in terms of regulations, applicable law and standards of professional conduct and practice, and institutional commitments. The IRB shall include persons knowledgeable in these areas.

b. The membership shall be diverse, and shall include consideration of race, gender, cultural backgrounds, clinical experience, healthcare experience and sensitivity to such issues as community attitudes to assess the research submitted for review.

c. There shall be at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. There shall be one member who has no affiliation with this institution, either self or family member.

3. Composition of the Board

a. Regular members: The backgrounds of the regular members shall be varied in order to promote complete and adequate reviews of the types of research activities commonly reviewed by the IRB. Regular members must include:

(1) Nonaffiliated member(s): The nonaffiliated member(s), who can be either scientific or nonscientific reviewers, should be knowledgeable about the local community and be willing to discuss issues and research from that perspective.

(2) Scientific members: Most IRBs include physicians and Ph.D. level physical or biological scientists. Such members satisfy the requirement for at least one scientist. When the IRB encounters studies involving science beyond the expertise of the members, the IRB may use a consultant to assist in the review, as provided by 21 CFR 56.107(f).

(3) Nonscientific member: The intent of the requirement for diversity of disciplines is to include members whose main concerns are not in scientific areas. Therefore, nonscientific members are individuals whose education, work, or interests are not solely in medical or scientific areas.

b. Alternate members: An alternate member(s) may be designated, as needed, for a regular voting

member(s). The appointment of alternate member(s) will be based on expertise similar to that of the regular voting member(s). An alternate member may vote only when the regular voting member is absent.

c. Representatives of special groups of subjects: When certain types of research are reviewed, members or consultants who are knowledgeable about the concerns of certain groups or types of research may be required. In addition, HCA Midwest Division's IRB will have at least one children's advocate and one prisoners' advocate on the IRB to deliberate on issues of these vulnerable populations.

d. Chairperson: The individual IRB Chairperson should be a highly respected individual, from within or outside HCA Midwest Division, fully capable of managing his/her IRB obligations and the matters brought before it with fairness and impartiality.

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

4. Responsibility

HCA Midwest Division is responsible for ensuring that the IRB has adequate resources to identify and recruit qualified potential members. The Institutional Official is responsible for appointing new members.

IRB Staff (or equivalent) is responsible for educating and new IRB members.

IRB Staff and Chairperson are responsible for determining when consultants are needed. When consultants are needed, it is the responsibility of the IRB staff to find the appropriate consultants, provide him/her with all of the necessary information (the same information provided to the members), and present his/her report to the IRB or schedule him/her to attend the meeting.

5. Applicable Regulations And Guidelines

45 CFR 46.107
21 CFR 56.107
FDA Information Sheets, FAQ section II, questions 14, 15.

B. MANAGEMENT OF THE IRB

1. Policy

The management of IRB membership and oversight of member appointments, related activities, communications, and other administrative details are the responsibility of the IRB Administrator.

2. Term

Appointment of IRB members is for five years. Each member must attend at least 70% of scheduled meetings per year in order to maintain membership status. A Chairperson for the IRB is also appointed for a five-year term. Members (including the Chairperson) may serve successive, additional terms upon concurrence of HCA Midwest Division's Institutional Official.

If for any reason an IRB member resigns, the Institutional Official shall appoint another individual to serve as a replacement.

3. Appointments

The Midwest Division Vice President of Quality/Risk Management and IRB Administrator have the authority to appoint members to the IRB.

4. Resignations and Removals

A member may resign before the conclusion of his/her term. The vacancy will be filled as quickly as possible. A member may also be removed by the Institutional Official and/or the Division Vice President of Quality and Risk Management, under certain circumstances.

5. Responsibility

IRB Administrators are responsible for day-to-day management of IRB operations. IRB Chairperson (or designee) is responsible for management of IRB meetings. IRB members, including Chairpersons, are responsible for issues relevant to meeting conduct and review of research.

C. DUTIES OF IRB MEMBERS

1. Policy

Each IRB member's primary duty is the protection of the rights and welfare of the individual human beings volunteering to participate in research. The IRB member must understand that he or she is not serving on the IRB to expedite the approval of research, but rather to be a gatekeeper between the Principal investigator and the research subjects. In order to fulfill their duties, IRB members are expected to be knowledgeable about the regulations governing human subject's protection, biomedical and behavioral research ethics, and the policies of HCA Midwest Division regarding human subject's protection.

2. Duty to the Institution

The IRB must be perceived to be fair and impartial, immune from pressure either by the institution's administration, the Principal investigators whose protocols are brought before it, or other professional and nonprofessional sources. Members must not allow their own interest to supersede their duty to protect the rights and welfare of research subjects.

3. Term of Duty

Regular IRB members and Chairpersons are expected to commit to a five-year term and to fulfill certain duties during that time. These duties will be described prior to appointment and each IRB member is expected to fully understand the duties of IRB members prior to accepting appointment as an IRB member.

4. Specific Duties

All members are expected to review the materials provided, regardless of affiliation or specialty area:

a. Nonaffiliated member(s): Nonaffiliated members are expected to provide input regarding their local community and/area of advocacy, and be willing to discuss issues and research from that perspective.

b. Non-scientific members: Nonscientific members are expected to provide input on areas relating to their knowledge, expertise and experience, professional and otherwise. For example, members who are lawyers might present the legal views of specific areas that may be discussed, such as exculpatory language or state requirements regarding consent. Non-scientific members should advise the IRB if additional expertise in a non-scientific area is required to adequately assess a protocol.

c. Scientific members: Scientific members are expected to contribute to the evaluation of a study on its scientific and statistical merits and standards of practice. These members should also be able to advise the IRB if additional expertise in a non-scientific area is required to assess a protocol.

d. Chairperson: In addition to the above responsibilities, Chairpersons chair meetings of the IRB. (Chairpersons may perform expedited review or delegate to an appropriate voting member when appropriate.) They are also empowered to suspend the conduct of a clinical trial if it is deemed to place individuals at unacceptable risk, pending review. The Chairperson is also empowered, pending IRB review, to suspend the conduct of a study if he/she determines that a Principal investigator is not following IRB requirements.

e. The Chairperson may appoint a Co-chairperson or Associate or Vice Chairperson to assist or act on behalf of the Chairperson in particular IRB matters and at IRB meetings. The Chair person also may delegate any of his/her responsibilities as appropriate to other qualified individual(s). Such documentation must be in writing and maintained by the IRB Administrative Office.

5. Responsibility

The IRB Administrator (or equivalent) is responsible for clearly articulating all IRB members' duties to potential and current IRB members. IRB Members are responsible for fulfilling their duties as specified.

6. Applicable Regulations And Guidelines

OHRP IRB Guidebook
FDA Information Sheets FAQ, section II, question 17.

VI. FUNCTIONS & OPERATIONS

A. RESEARCH SUBMISSION REQUIREMENTS

1. Policy

IRB members must often rely solely on the materials submitted by Principal investigators to conduct initial and continuing review of research projects. Therefore, this material must provide IRB members with enough information about a study to assess if it adequately meets criteria for approval. A submitted protocol will be scheduled for IRB review when staff has determined that the information and materials submitted present an adequate description of the proposed research.

2. Submission Requirements for Initial Review

a. Required: Principal investigators applying for initial approval of proposed research must submit:

(1) An Application for Behavioral Study Review or an Application for Bio-Medical Study Review,
(2) A detailed research protocol (federal grant application will suffice for this),
(3) Informed consent form(s),
(4) All surveys, questionnaires, etc. that are indicated in the protocol,
(5) Recruitment materials (e.g. flyers, advertisements, copy of radio advertisements),
(6) Data and Safety Monitoring Plan, or information regarding the Data and Safety Monitoring Board (if one has been established),
(7) Updated CV, and
(8) Certification of education in the protection of human subjects (if the IRB does not have this on file).

b. In addition, applicants may be required to submit:

(1) Supplemental Application for Research Involving Prisoners
(2) Supplemental Application for Research Involving Children
(3) Supplemental Application for Research Involving Pregnant Women, Human Fetuses, and Neonates
(4) Supplemental Application for Research Involving DNA, Tissue, Sample Banks
(5) Supplemental Application – Investigational Drug Information Record
(6) Supplemental Application – Indications for IND and IDE
(7) Financial Disclosure Form
(8) Statement of Investigator form (FDA 1572)
(9) Investigator's Brochure
(10) Grant Application, if federally funded
(11) If outside facilities or agencies are used as research sites, letters of agreement. If these facilities have an IRB; include a copy of the letter of approval for this study.
(12) Application for Expedited Review

3. Submission Requirements Throughout the Study's IRB Approval Period

1) During the approval period, Principal investigators must submit documentation to inform the IRB about changes in the status of the study including, but not necessarily limited to:

a) Amendments/Addenda to Approved Protocols/Consent Forms
b) Reports of serious or unexpected adverse events
c) Deviations from the protocol (protocol violations)

b. Amendments/Addenda to Approved Protocols/Consent Forms

The following should be submitted to the IRB office:

(1) An Application for a Protocol Amendment or Addendum,
(2) Revised Protocol,
- One version with track changes indicating where the protocol has been changed and
- One clean version

(3) Revised Consent form, if necessary,
- One version with track changes indicating where the form has been changed, and
- One clean version

(4) Application for Expedited Review, if applicable.

c. Serious Adverse Events

Principal investigators must report SAEs, using the SAE Report Form, to the IRB within 48 hours of discovery, and 24 hours for deaths. The SAE Form requires the Principal investigators to make their best estimate, at the time of reporting, of the causal relationship between study participation and the SAE. The Principal investigator should attempt to obtain records (which may include physicians' notes, hospital discharge summaries, biopsy, x-ray or other laboratory results, autopsy findings, etc.) to help clarify the nature of the SAE.

The descriptions below should be used to grade the SAE's study-relatedness:

(1) Not related:
Clearly due to extraneous causes (e.g., underlying disease, environment)
(2) Unlikely (must have 2):
a. Does not have a temporal relationship to intervention
b. Could readily have been produced by the participant's clinical state
c. Could have been due to environmental or other interventions
d. Does not follow a known pattern of response to intervention
e. Does not reappear or worsen with reintroduction of intervention
(3) Possibly (must have 2):
a. Has a reasonable temporal relationship to intervention
b. Could not readily have been produced by the participant's clinical state
c. Could not readily have been due to environmental or other interventions
d. Follows a known pattern of response to intervention
(4) Probably (must have 3):
3a, b, c, d above
e. Disappears or decreases with reduction in dose or cessation of intervention
(5) Definitely (must have all 5):
3a, b, c, d above
e. Disappears or decreases with reduction in dose or cessation of intervention and
f. Recurs with re-exposure

As noted on the SAE form, the Principal investigator must also recommend to the IRB whether the SAE necessitates a change in the study protocol, and/or the consent form. The IRB will make the decision to accept/reject these proposed changes or to require new ones. Principal investigators should use their best judgment in terms of what would best protect and inform study participants.

Principal investigators are also responsible for reporting the following to the IRB in a timely

fashion: new information that may impact the risk/benefit ratio of the study; irregularities in conducting the study, Data and Safety Monitoring Board reports, and copies of all external SAE reports.

d. Protocol Deviations

It is the responsibility of the Principal investigator to submit reports of all protocol deviations to the IRB after their occurrence. The following should be submitted to the IRB office:

(1) Deviation Form

(2) Revised Protocol, if necessary
- One version with track changes indicating where the protocol has been changed, and
- One clean version

(3) Revised Consent form, if necessary
- One version with track changes indicating where the form has been changed, and
- One clean version

(4) SAE Form, if necessary.

4. Submission Requirements for Continuing Review

For continuing reviews, the following should be submitted to the IRB office (at least 60 days in advance of the IRB meeting held prior to the study's expiration, and two weeks in advance of the study's expiration for an expedited review):

a. Application for Continuing Review to include:

1. The number of subjects accrued;

2. A summary of any unanticipated problems and available information regarding adverse events

3. A summary of any withdrawal of subjects from the research since the last IRB review;

4. A summary of any complaints about the research since the last IRB review;

5. A summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last IRB review;

6. Any relevant multi-center trial reports to include:

(i) A statement indicating what information (e.g., study-wide adverse events, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;

(ii) The date of the review; and

(iii) The monitoring entity's assessment of the information reviewed.

7. Any other relevant information, especially information about risks associated with the research;

b. Progress Report
c. Approved Protocol (if requesting revisions, one clean version and one with track changes)
d. Approved Consent Form (if requesting revisions, one clean version and one with track changes)
e. List of all SAEs since the last review
f. Protocol Summary
g. Additional forms (when necessary) for protocol/consent form modification
h. Application for Expedited Review (when applicable)

When changes in the protocol are to be made at the time of continuing review, the Continuing Review Form should be accompanied by an Application for a Protocol Amendment/Addendum, which details the proposed changes as well as an explanation of the rationale for the change, and an estimate of whether the change affects the risk/benefit ratio of the project. In addition to the form, the Principal investigator should submit a revised protocol, and one with track changes. If the changes require revision to the informed consent form, the Principal investigator should also submit one clean version and one with track changes.

5. Special Reporting Requirements

In special circumstances, determined at the time of review, the IRB may stipulate that some type of review should take place more frequently than once a year. When special reporting requirements are set as a condition of approval, the Principal investigator must submit either the required information or a progress report, as indicated in the approval letter. For example, if the IRB is concerned with the recruitment rate of a study at the time of its continuing review, the IRB may stipulate in its approval that enrollment should be reviewed again in six months. Therefore, in six months the Principal investigator must submit a letter to the IRB informing it of the study's current enrollment.

6. Submission Requirements for Final Review

When a project has been completed or when the Principal investigator's participation in a project has ended, the Principal investigator must submit a final report summarizing all activity carried out through the protocol.

For a Final Review, a Principal investigator must submit the following to the IRB:
a. Application for Final Review,
b. Summary of Research Results, and
c. Any publications resulting from the study.

7. Submission Requirements for Study Close-Outs

If for any reason a Principal investigator decides to close-out a study before its completion as per protocol, the Principal investigator must submit a final report summarizing all activity carried out through the protocol, and the reasons for the study's closure.

To Close-Out a study, a Principal investigator must submit the following to the IRB:
a. Application for Final Review,
b. Summary of all activity carried out through the protocol,
c. Reasons for the study's closure, and
d. A draft of a letter informing subjects' of the study's closure, and how they will be affected by

it, if necessary.

8. Submission Requirements for Exemptions from IRB Review

For studies, which are deemed to be exempt from IRB review by 45 CFR 46.101(b), a Principal investigator must submit the following to the IRB Department:

a. Application for Exemption from IRB Review,
b. Protocol (can follow the 'Exempt Protocol Template'),
c. Informed Consent, if necessary,
d. Information Sheet, if necessary, and
e. All questionnaires/measures to be used, if applicable

9. Action Taken if Documentation is Not Adequate or Additional Information is Required

If the IRB or IRB staff determines that the submitted documents are not adequate, Principal investigators may be required to submit additional information, or their presence may be required to answer questions or explain the details of the study. Incomplete submissions will not be reviewed by the IRB.

10. Responsibility

The IRB Administrator is responsible for maintaining current research submission requirements for interested Principal investigators and for preliminary triage of non-routine submissions. IRB Administrator is responsible for preparing member review materials and reviewing submission elements.

11. Applicable Regulations and Guidelines

45 CFR 46.115
21 CFR 56.108 (a)(4)
21 CFR 312, 812
ICH Good Clinical Practice (GCP) Guideline

B. IRB MEETING ADMINISTRATION

1. Policy

Except when an expedited review procedure is used, or the study qualifies for exempt status, the IRB will review all proposed research at convened meetings at which a quorum is present. The IRB will meet every four weeks, or as necessary (at a frequency determined by the IRB Chairperson and the IRB Administrator) to adequately review initial and continuing research.

2. Quorum

a. A quorum is defined as one half of the number of regular members plus one.

b. A quorum includes at least one member whose primary concerns are in scientific areas, and one member whose primary concerns are in nonscientific areas.

c. Staff and/or special consultant(s) will not be used to establish a quorum.

3. Primary Reviewer System

A primary reviewer system may be used for new submissions, protocols involving vulnerable populations, protocol amendments, and for continuing reviews.

Although the primary reviewer system is utilized, all IRB members will receive all submission materials. For protocols involving vulnerable subject populations, the IRB Chairperson and/or Administrator will assign the advocate for the particular vulnerable subject population as the primary reviewer. All IRB members will be responsible for an in-depth review of the protocol and other submission materials. In addition, the primary reviewer will be responsible for an in-depth review of the protocol as it relates to the vulnerable subject population.

For initial continuing reviews, and amendments, the IRB Chairperson and/or Administrator may assign a primary reviewer, to provide an in-depth review of the study. The IRB member with the most relevant expertise regarding a specific protocol will be assigned as the study's primary reviewer. This member will receive a copy of the complete protocol including any modifications previously approved by the IRB, in addition to the rest of the submission materials. All other IRB members will receive same information. Upon request, any IRB member will have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. The primary reviewer will be responsible for an in-depth review of the protocol and the initial or continuing review information, and will lead the discussion regarding the protocol at the convened meeting.

4. Meeting Materials Sent Prior to IRB Meetings

All IRB members will be sent the required review documentation sufficiently in advance of the meeting to allow time for adequate review. These include:

a. Agenda: a meeting agenda will be prepared by the IRB Administrator and distributed to IRB members prior to each meeting. A copy of the agenda and attached materials will be maintained on file in the IRB office.

b. Educational material: All members will be provided with educational material, such as an article, guidance document, or selected text from the SOPs/regulations/etc. to keep them apprised of current human research protections issues.

c. Minutes of previous meetings: All members will be provided with previous meeting minutes to review and comment. Minutes will be voted upon during the following meeting to approve, require changes, or defer.

d. Reviewer materials: All IRB members will receive a complete copy of the submitted materials for each study. Upon request, any IRB member will have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

e. Table of new serious adverse events.

f. Summary of Recent Expedited Reviews.

g. Summary of Recent Exemptions from IRB Review.

h. A packet of Reviewer Forms to guide the IRB members in their review of each protocol.

5. Minutes

a. Federal regulations for the protection of human subjects [45 CFR 46.115(a) (2)] require that "Minutes of IRB meetings… shall be in sufficient detail to show attendance at the meeting; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution." These requirements are the minimum. Quality minutes should enable a reader who was not present at the meeting to determine exactly how and with what justification the IRB arrived at its decisions. IRB members representing vulnerable populations should be noted in the minutes.

b. Criteria for approval:

1. Determinations for approval by the IRB must include all of the following:
    a. An analysis of the potential sources of risk (*i.e.*, physical, psychological and social/economic), with special mention of additional risk posed to vulnerable populations (specifically prisoners, pregnant females and children). Note, 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;
    b. A favorable opinion that the risks to subjects are minimized (*i.e.*, including the use of procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes);
    c. A favorable opinion that the risks to subjects are reasonable in relation to anticipated benefits to subjects and/or the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive in the absence of the research). Similarly, the IRB should not consider payment to research subjects a benefit for purposes of this evaluation.
    d. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons (see the Recruitment of Vulnerable Subject Populations Policy, QM.RES.007). The inclusion/exclusion criteria for the study should impose fair and equitable burdens and benefits and recruitment efforts should be unbiased towards any population or sub-population;
    e. Unless meeting such criteria for waiver or partial waiver, informed consent will be sought from each perspective subject or the subject's legally authorized representative, in accordance with, and to the extent required by statute (see the Informed Consent IRB Review Policy, QM.RES.003);
    f. Unless meeting such criteria for waiver , informed consent will be appropriately documented in accordance with, and to the extent required by, statute (see the Informed Consent IRB Review Policy, QM.RES.003);
    g. When appropriate, the research plan makes adequate provision to protect the privacy of subjects and to maintain the confidentiality of data;

h. When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of the subjects;
i. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
j. Documentation of the above must be in the meeting minutes.

c. Recording: The IRB Administrator will take notes of each meeting. An audio recording of each meeting may also be used if appropriate to aid in the preparation of written minutes, but the written meeting minutes will be the official record. Minutes will be written in sufficient detail to show the following:

1. Meeting attendance; including names of attendants, their affiliation status with HCA Midwest Division, status as scientist/non-scientist, and their role on the IRB (i.e., Children's Advocate).

2. Actions taken by the IRB on each agenda item requiring full IRB action, including, the basis for requiring changes in or disapproving the research, the level of risk and the approval period; and special considerations for Parts B, C and D of the Common Rule.

3. Summary of the discussion of controverted issues and resolution;

4. Voting results, including number for, against, abstentions (reason why) and members who recused themselves and reasons for refusals. Members who abstain themselves due to a conflict of interest may not be counted toward quorum requirements or be counted as among the majority of; members necessary to constitute a quorum.

5. Use of the primary reviewer system.

d. Approval: Minutes will be distributed to members within two weeks of the IRB meeting for review and approval. Corrections requested by the IRB will be made by the IRB Administrator or designee. The IRB Administrator shall sign and date the final, approved minutes at the next convened meeting following vote of acceptance of the minutes.

e. The IRB Administrator will maintain copies of the minutes, as well as the agenda and pertinent materials on file. One hard copy and one electronic copy will be maintained.

f. A majority of members must vote in favor of an action in order for that action to be accepted by the IRB. Only regular and alternate members acting in place of absent regular members may vote. The vote will be recorded in the minutes. Members with a conflict of interest will recuse themselves from the discussion and voting and such will be noted in the minutes. Maintenance of a quorum after refusals will be noted in the minutes.

6. Telephone and/or Video-Conferencing

a. Convened meetings using speakerphone: Should a member not be able to be physically present during a convened meeting, but is available by telephone, the meeting can be

convened using a speakerphone. The member who is not physically present will be connected to the rest of the members via speakerphone. In this manner, all members will be able to discuss the protocol even though a member is not physically present. Members participating by such speakerphone call may vote, provided they have had an opportunity to review all the material the other members have reviewed.

b. Meetings Conducted Via Telephone or Video Conference Calls: Meetings may also be convened via a telephone conference call. A quorum (as defined above) must participate for the conference call meeting to be convened. To allow for appropriate discussion to take place, all members must be connected simultaneously for a conference call to take place -- "telephone polling" (where members are contacted individually) will not be accepted as a conference call.

7. Voting

a. Members of the IRB vote according to the criteria for approval. Members also will determine level of risk, and the frequency of review for each protocol. Members may vote for, against, or abstain from voting.

b. Members not present at the convened meeting, or not participating in a conference call, may not vote on an issue discussed during a convened meeting (no voting by proxy).

8. Responsibility

IRB Administrator is responsible for IRB meeting procedural conduct and documentation. IRB Chairperson (or designee) is responsible for IRB meeting review conduct and leadership.

IRB Chairperson or Administrator is responsible for assigning primary reviewers for initial submissions, protocols involving vulnerable subject populations, and continuing reviews.

9. Applicable Regulations And Guidelines

45 CFR 46.103, 46.108
21 CFR 56.108, 56.109
FDA Information Sheets, 1998
OHRP Guidance on Continuing Review, July 11, 2002

C. ADMINISTRATIVE REVIEW AND DISTRIBUTION OF MATERIALS

1. Policy

The efficiency and effectiveness of the IRB is dependent upon each member's receipt of materials for review. Each member should have adequate time for thorough assessment of each proposed study, and documentation that is complete and clear enough to allow for an adequate assessment of study design, procedures, and conditions.

2. Exemptions

The IRB Administrator will review Claims for Exemption submitted by Principal investigators in consultation with the IRB Chairperson. If granted, such Claims of Exemption will be filed, and a

report of exemptions provided to the full IRB.

3. Incomplete Submissions

Incomplete applications will not be accepted for review. Incomplete submissions will be returned and will not be scheduled for review until the Principal investigator has provided all necessary materials as determined by the IRB Administrator. The IRB Administrator will notify the submitting Principal investigator of any documentation or additional information necessary for the application to be scheduled for review.

4. Scheduling for Review

Complete applications will be placed on the agenda for the earliest meeting possible for review by the full IRB as described in IRB Meeting Administration.

5. Distribution to Members Prior to IRB Meetings

Copies of application materials described in Research Submission Requirements will be distributed to all IRB members, generally at least seven (7) days prior to the meeting. Each regular member of the IRB attending the meeting will receive a copy of the initial application material. If Consultants are scheduled to attend, they will only receive copies of material that pertain to their requested input. The originals of submission materials will be retained in the IRB Office and available for the IRB meeting.

6. Confidentiality

All material received by the IRB will be considered confidential and will be distributed only to meeting participants for the purpose of review. All application materials will be stored in an IRB study file with access limited to the IRB members and staff. Consultants and visitors will be expected to sign Confidentiality Agreements.

7. Responsibility

The IRB Administrator is responsible for providing complete review material packets to IRB members and other relevant parties. IRB Chairperson (or designee) is responsible for supporting and assisting the IRB Administrator in determining priority of submissions.

8. Applicable Regulations And Guidelines

21 CFR 56.109
45 CFR 46.109

D. DOCUMENTATION AND DOCUMENT MANAGEMENT

1. Policy

a. IRB files must be maintained in a manner that contains a complete history of all IRB actions related to review and approval of a protocol, including continuing reviews, and amendments. All records regarding a submitted study (regardless of whether it is approved) must be retained in an appropriate manner as required by regulatory requirements and/or institutional policy.

b. Records must be accessible for inspection and copying by authorized representatives of the Sponsor, funding department or agency, regulatory agencies and institutional auditors at reasonable times and in a reasonable manner.

2. Document Retention

a. The IRB Office will retain all records regarding an application (regardless of whether it is approved) for at least three (3) years. For all applications that are approved and the research initiated, the IRB Office will retain all records regarding that research for at least three (3) years after completion of the research.

b. Study-related documents: Adequate documentation of each IRB's activities will be prepared, maintained and retained in a secure location. Retained documents include:

1. Copies of all original research protocols reviewed, scientific evaluations, if any, that accompany the proposals, approved consent documents, progress reports submitted by Principal investigators and reports of adverse events occurring to subjects and reported deviations from the protocol.
2. Agendas and minutes of all IRB meetings.
3. Copies of all submitted monitoring reports, site visit reports and other continuing review activities.
4. Copies of all correspondence between the IRB and the Principal investigators.
5. Statements of significant new findings provided to subjects.
6. Reports of any complaints received from subjects.

3. IRB Administration Documents

a. The IRB Office will maintain and retain all records regarding IRB administrative activities that affect review activities for least three (3) years. The IRB Office will retain all records regarding protocols that are approved and the research initiated for at least three (3) years after completion of the research. These policies and procedures apply to all controlled documents used in the submission, initial review, and continuing review of research submitted to the IRB.

b. Rosters of regular and alternate IRB members identified by name, earned degrees, representative capacity, and indications of experience sufficient to describe each regular and alternate member's chief anticipated contribution to the IRB's deliberations; and any employment or other relationship between each member and the IRB and HCA Midwest Division (e.g., full-time employee, part-time employee, member of Board of Directors, paid or unpaid consultant). Current and obsolete membership rosters will remain in the IRB Office and then archived.

c. Changes in the IRB's membership are to be reported to OHRP as they occur.

d. A current copy of the Standard Operating Policies and Procedures should be maintained in the IRB Office.

e. Delegation of specific functions, authorities, or responsibilities by the IRB Chairperson must be documented in writing and filed in the IRB Office.

4. Destruction of Copies

All material received by the IRB members, which is considered confidential and in excess of the required original documentation and appropriate controlled forms, will be destroyed by a method such as shredding the paper.

5. Archiving and Destruction

After 3 years, all documents and materials germane to IRB determinations will be archived according to institutional policy. Archiving policies of HCA Midwest Division will determine when such archived records may be destroyed.

6. Responsibility

The IRB Administrator is responsible for maintaining complete files on all research reviewed by or submitted to the IRB and for all applicable regulatory compliance requirements.

7. Applicable Regulations And Guidelines

45 CFR 46.103,115
21 CFR 56.115

VII. TYPES OF IRB REVIEW/IRB MEETING PROCEDURES

A. HUMAN SUBJECTS RESEARCH

1. Policy

The IRB Chairperson, with assistance from the IRB Administrator, will determine whether research constitutes human subjects research. Principal investigators must submit a protocol to the IRB office, so that the IRB Chairperson and Administrator can make an independent determination if the research involves human subjects or not.

2. Definition of 'Research'

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

3. Definition of 'Human Subject'

HHS regulations define *human subject* at 45 CFR 46.102(f) as follows: *Human Subject* means a living individual about whom a Principal investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

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

4. Determining if a Protocol Involves Human Subjects Research

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. HCA Midwest Division interprets *obtaining* to include a Principal investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the Principal investigator.

HCA Midwest Division does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 36.102(f) if the following conditions are both met:

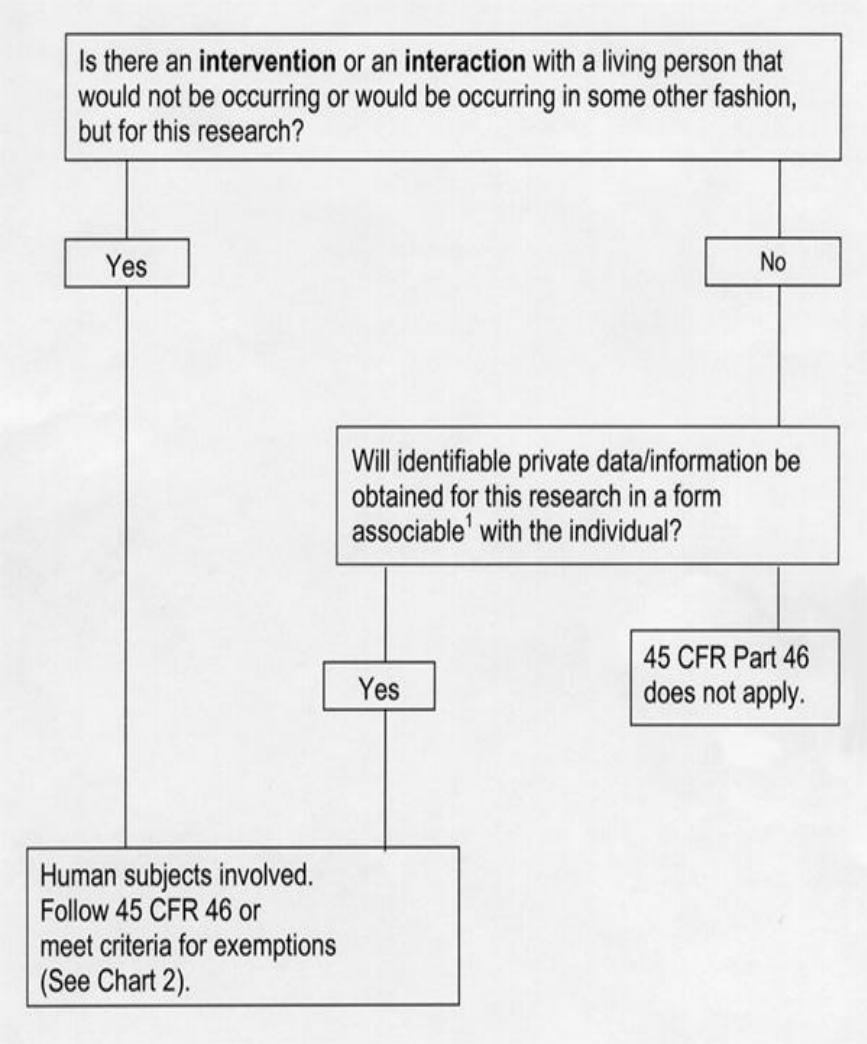
a. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
b. the Principal investigator cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
    1. the key to decipher the code is destroyed before the research begins;
    2. the Principal investigator and the holder of the key enter into an agreement prohibiting the release of the key to the Principal investigators under any circumstances, until the individuals are deceased (the IRB does not need to review and approve this agreement);
    3. 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 Principal investigators under any circumstances, until the individuals are deceased; or
    4. there are other legal requirements prohibiting the release of the key to the Principal investigators, until the individuals are deceased.

This policy applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected n the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

In some cases a Principal 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 Principal 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 under the HHS regulations. Unless this human subjects research is determined to be exempt under HHS regulations at 45 CFR 46.101(b), 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 under HHS regulations at 45 CFR part 46.116(c) or (d).

5. Human Subjects Research Decision Chart



[1]That is, the identity of the subject is or may readily be ascertained or associated with information.

6. Responsibility

The IRB Chairperson, with assistance from the IRB Administrator, will determine whether specific research protocols constitute human subjects research.

7. Interaction with Other Research Related or Institutional Committees

Use of a centralized IRB review process is consistent with the existing IRB regulations. Section 56.114 (21 CFR 56.114 Cooperative Research) provides, "institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort." When this rule was proposed, the preamble to the proposed rule indicated that the purpose of this section is "to explicitly reduce duplicative review of multi-institutional studies." The preamble to the final rule also stated that "the purpose of this section is to assure IRBs that FDA will accept reasonable methods of joint

review." Physical proximity of an IRB to a research site is not necessarily of significance, provided that the IRB is competent to understand the local context of the research. As stated in 21 CFR 56.107(a), this would require sensitivity to community attitudes, familiarity with the standards of professional conduct and practice where the research takes place, and knowledge about local laws and regulations applicable to the study. Source: http://www.fda.gov/cber/gdlns/irbclintrial.htm.

Engaged (Participating) in Research - Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OHRP with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). An institution becomes "engaged" in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes [45 CFR 46.102(d), (f)]. An institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award.

National Cancer Institute

The NCI offers an IRB available for cooperative review of NIH funded studies to alleviate the duplication of review of portions of NIH funded research. HCA facilities may amend the above procedures and follow the guidelines posted at www.NCICIRB.org in its review of its NCI studies.

Data Safety Monitoring Boards:

Sponsor-Investigators with a high volume of self-sponsored research projects should establish an independent data monitoring committee for those self-sponsored protocols to exercise oversight of the clinical investigation and the informed consent process. An independent sponsor may also establish Data Safety Monitoring Boards. Information from these committees should be provided to the IRB in order to perform continuing review.

8. Applicable Regulations And Guidelines

45 CFR 46.102(d)
45 CFR 46.102(f)
OHRP Guidance on Research Involving Coded Private information or Biological Specimens, August 10, 2004

B. EXEMPTIONS FROM IRB REVIEW

1. Policy

The IRB Chairperson, with assistance from the IRB Administrator, will determine whether

research protocols qualify as exempt from IRB review, under 45 CFR 46.101(b). Principal investigators must submit a protocol to the IRB office, so that the IRB Chairperson and Administrator can make an independent determination if the research qualifies as exempt or not. The Principal investigator should also submit the following if applicable: (1) informed consent document; (2) information sheet; (3) questionnaires/measures.

Federal regulations permit an IRB to provide for exemption from IRB review for certain kinds of research if specific conditions are met. *Research that is granted exemption from IRB review may still require formal informed consent of each participant. Additionally, exemption from IRB review does not automatically imply the criteria for a HIPAA waiver of authorization which must be determined independently based on its own criteria.* Even if a protocol is eligible under federal regulations for Exempt Status, the IRB may choose to review the protocol in accordance with its usual procedures. No studies involving the use of investigational drugs, devices or biologics will be granted Exempt Status.

Exemptions do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization. In addition, survey research, involving children, and research under FDA jurisdiction (except in emergency circumstances) are *not* exempt from federal regulations.

A claim of exemption does not automatically mean the IRB will grant exempt status. The IRB is not obligated to grant exemptions to proposed research. In fact, the IRB may require review of all such activities, whether funded or not, to ensure that the research meets the federal requirements for a "Claim of Exemption." Therefore, in order to fulfill the requirement for the proper review of research, Principal investigators cannot "self-exempt" from IRB review.

If a protocol is determined to be Exempt, Principal investigators will not be required to submit materials to the IRB. However, should any additional study procedures change that could affect the exempt status of the study, the Principal investigators should contact the IRB office. The IRB Administrator will review the change and determine if the Exempt status has changed. If the IRB Administrator determines that the study's Exempt status has changed, the information will be forwarded to the IRB Chairperson for final determination. If the IRB Chairperson determines that the study is no longer Exempt, than the study will undergo either an expedited (if eligible) or full-board review.

2. Research Exempt from IRB Review

Research in categories described below is considered exempt from IRB review with the exceptions as noted:

a. Research conducted in established or commonly accepted educational settings, involving normal education practices, such as:
   - Research on regular and special education instructional strategies, or
   - Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

b. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
   - Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and
   - Any disclosure of the human subjects responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

- **Note: This does not apply to research involving children except for research involving observations of public behavior when the Principal investigator does not participate in the activities being observed.**

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

d. Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the Principal investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
   - **NOTE: Chart reviews may only be considered exempt if patient/subject identifiers are NOT retained by the Principal investigator.**

e. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
   - Public benefit or service programs;
   - 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.
   - Taste and food quality evaluation and consumer acceptance studies,
   - If wholesome foods without additives are consumed or
   - 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.

3. Responsibility

The IRB Chairperson is responsible for evaluating applications for exemption from IRB review. IRB Administrator is responsible for providing consultation in the review of claims of exemption.

4. Applicable Regulations And Guidelines

45 CFR 46.101
21 CFR 56.104, 105

C. EMERGENCY EXEMPTION FROM PROSPECTIVE IRB APPROVAL

1. Policy

The IRB acknowledges that there are rare circumstances in which the normal review process must

be circumvented. These are instances where unforeseeable urgent clinical needs or opportunities in individual patients require immediate action. A request for emergency approval may be made by calling the IRB office.

The attending physician must discuss the request for emergency use with HCA Midwest Division's Medical Director. The attending physician is the individual who will be held responsible for fulfilling the requirements for follow-up reporting to the IRB.

Emergency approval will not be issued for routine applications submitted to the IRB with insufficient time to meet a deadline mandated by the Principal investigator or a funding agency.

Treatment IND (Investigational New Drug) or IDE (Investigational Device Exemption) protocols for which the Principal investigator knows in advance that more than one patient is to be entered into the study are not considered appropriate for emergency approval requests. Such applications should be submitted for full Board review.

Many protocols involving investigational drugs or devices are funded by NIH. The NIH Office for the Protection of Research Risks, which was succeeded by the DHHS Office of Human Research Protections, determined in 1991 that "Whenever emergency care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity." This explanation does not preclude providing an investigational product on an emergency basis with approval by the IRB Chairperson. This type of approval, however, does not meet NIH's regulatory definition of action taken at a convened meeting and, therefore, NIH does not allow submission of data from such cases as part of the NIH-FUNDED study.

2. Definition: Emergency Use

Emergency use is defined as the use of an investigational drug or biologic product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. Human subject research activities are not 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 may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity.

The emergency use provision of the FDA regulations is an exemption from prior review and approval by the IRB and allows for one emergency use of an investigational drug or biologic product without prospective IRB review.

3. Responsibility

The responsibilities, which accompany use of an investigational drug or device on an emergency basis include the following:

a. An investigational drug or device can only be dispensed on an FDA-approved protocol, held either by a sponsor or an individual physician. If a sponsor is willing to allow a physician to use an investigational drug or device on an emergency basis via their FDA-approved protocol, the sponsor still requires approval from an IRB. Agreement by the sponsor to ship a drug is usually accompanied by paperwork detailing the justification for use of the drug

and outlining reporting requirements after the patient has been treated.

b. The IRB Chairperson or designee (using consultants as appropriate, such as one of the facility department Medical Directors) may issue a letter acknowledging notification of emergency use of the test article, on a case-by-case basis. The Principal investigator should generate a letter to the IRB Chairperson describing the emergency-use situation, documenting compliance with the specific FDA requirements for emergency use. The notification to the IRB must occur prior to or within five days of use of the test article. The IRB Chairperson or designee will review the letter and confirm that an emergency situation exists and there is not sufficient time to convene a full-board IRB meeting. A written report is to be submitted for full IRB information within 10 working days of the Emergency Request. Acknowledgement by the IRB Chairperson should not be construed as IRB approval. Its purpose is to initiate a follow up file to ensure that the required notification/report is submitted.

c. The patient must understand the investigational nature of the test article. Informed consent must be obtained; however, the consent form is not a standard research consent form. In most cases, the sponsor will supply a consent form. The IRB is not involved in the review or approval of the consent form if the situation meets the criteria for emergency use.

4. Informed Consent for Emergency Use

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

a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
c. Time is not sufficient to obtain consent from the subject's legal representative.
d. 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 Principal investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical Principal investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The Principal investigator must notify the IRB within 5 working days after the use of the test article

5. Applicable Regulations And Guidelines

21 CFR 56.102(d)
21 CFR 56.104(c)
21 CFR 50.23(a)
21 CFR 50.23(c)

D. EXPEDITED REVIEW

1. Policy

An expedited review procedure consists of a review of research involving human subjects by the Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the IRB (may also include contracted consultants). These policies and procedures apply to all research submitted to the IRB that qualifies for expedited review.

The categories of research that may be reviewed by the IRB through an expedited review procedure include research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the specific categories listed in the regulations at Federal Register Volume 63, No 216. In addition, an expedited review procedure can be used to review minor changes in previously approved research during the period for which approval is authorized.

2. Definition of Minimal Risk

Minimal risk is defined as "...the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests…."

3. Cautions

a. The activities listed should not be deemed to be of minimal risk simply because they are included on the list of eligible research. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure. The IRB reserves the right to require full board review of any application.

b. 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. Lastly, the expedited review procedure may not be used for classified research involving human subjects.

4. Categories of Research That May Be Reviewed Via the Expedited Review Procedure

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, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

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

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and 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 nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 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 from surgical, diagnostic, or therapeutic procedures made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral

history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 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.

   **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.*

(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.

5. Minor Changes to Previously Approved Research During the Period for which Approval is Authorized

The IRB may also use the expedited review procedure to review minor changes, which do not change the level of risk, in previously approved research during the period (of 1 year or less) for which approval is authorized.

At HCA Midwest Division, minor changes include the following:

(1) Informational revisions to the protocol or consent form, including but not limited to the following:
   a. changes in telephone/contact numbers
   b. addition or deletion of associates or staff
   c. changes to correct informational errors
   d. changes to correct typographical or grammatical errors
   e. changes to improve the clarity of statements
(2) Deletion of questions in a questionnaire
(3) Addition of non-sensitive questions to a questionnaire
(4) Addition of a standardized test/questionnaire
(5) Minor changes to the number of study participants
(6) Decrease in the amount of blood that is drawn or the frequency
(7) Decrease in the drug dosage or the frequency of drug administration
(8) Minor changes to the recruitment plan, or the inclusion/exclusion criteria
(9) Addition of, or changes to advertisements/recruitment letters
(10) Extension of the time period of the study to allow for follow-up interviews, or data analysis
(11) Extension of the time period for recruiting subjects
(12) Changes to the study title
(13) Minor procedural changes that do not impact participants
(14) Minor procedural changes that impact participants, but do not change the risk/benefit ratio

Any protocol revision that entails more than a minimal risk to the subjects must be reviewed by the full IRB at a convened meeting.

6. Authority of the IRB Chairperson

The IRB Chairperson (or designated reviewer) may exercise all of the authorities of the IRB, except that he/she may not disapprove the research. A research proposal may be disapproved only after review by the full IRB. For protocols involving vulnerable populations, the IRB Chairperson may consult with expert reviewers, or appropriate members of the IRB (such as the Children's Advocate or the Prisoner's Advocate), or designate the review to an appropriate IRB member.

7. Notification of the IRB

When the expedited review procedure is used, all regular members shall be informed of actions taken by the IRB at the next convened meeting. IRB members will be informed of expedited reviews with a summary of the review and a copy of the approval letter.

8. Documentation

If the study qualifies for expedited review, the IRB Chairperson or designee will document his/her determination of risk. The minutes of the next convened meeting will include documentation of the studies that were reviewed via expedited review and any issues discussed regarding questions that an IRB member had concerning the research reviewed.

9. Additional Items That May be Reviewed by the Chairperson or Designee

Approval of pending minor revisions, clarification: Revisions to consent documents and other documentation or clarifications submitted as a result of full IRB review and as a condition to final approval may be reviewed by the IRB Chairperson or his/her designee. Final approval will be issued providing the revisions, documentation or clarifications do not indicate or result in a change to the study or change the risk/benefit ratio.

10. Responsibility

The IRB Administrator is responsible for identifying submissions that qualify for expedited review, and for providing a summary of expedited reviews performed to IRB members at convened meetings. The IRB Chairperson or designee is responsible for conducting expedited reviews.

11. Applicable Regulations And Guidelines

Minimal Risk:	45 CFR 46.102
	21 CFR 56.102
Expedited Review:	45 CFR 46.110
	21 CFR 56.110
	FDA Information Sheets, 1998
	OHRP IRB Guidebook

E. FULL BOARD REVIEW

1. Policy

Full IRB review is required for most new applications submitted for review and approval. It is also required for most protocols seeking renewed approval 45 CFR 46.109(e) for the continuing review of human subjects research by an Institutional Review Board (IRB) at intervals appropriate to the degree of risk, but not less than once per year. Full IRB review may also be required for many amendments.

The convened meetings are generally held once every four weeks. A necessary quorum for the IRB to consider a proposal is a majority of the total membership, including a member whose primary concern is in a nonscientific area, before official actions may be taken at these meetings. The IRB will not have a member 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. An IRB member with a potential or real conflict of interest will leave the room during discussion and voting and the recusal will be noted in the IRB meeting minutes.

Appropriate Board members will be assigned by the IRB Chairperson and/or Administrator to be principal reviewers on one or more of the applications, for research involving vulnerable subject populations, and for continuing reviews. In cases where it is deemed necessary, consultants to the IRB may be asked to comment on a proposed research activity. Consultants will receive all of the same information that the IRB received, regarding the particular protocol, and will either be present at the meeting or provide a report to the IRB to be reviewed at the meeting.

When FDA-regulated research is reviewed, there shall be one member, or a consultant, who is a physician present, or the report of this member/consultant should be reviewed/discussed. If the IRB has any question for this member/consultant who is not present, the research will not be approved until the question has been answered to the IRB's satisfaction.

2. Voting

The IRB will decide by a majority of the members present:
(1) To approve the proposal (APPROVAL);
(2) To approve the proposal with minor, specific restrictions, conditions or modifications (APPROVAL WITH CONTINGENCIES); [This indicates that the requested changes will, upon submission, be directed to either the Chairperson or other designated IRB reviewer for final approval, and will not need to go back to the full IRB.];
(3) To defer the proposal, pending changes in the application or receipt of additional information from the Principal investigator or consultants to the IRB (DEFER/TABLE REVIEW); or
(4) To disapprove the proposal (DISAPPROVAL).

For approved research, the IRB will determine which activities require continuing review more frequently than every twelve months. More frequent reporting may be required to monitor the safety of a treatment protocol. It is at the Board's discretion to implement these measures. In general, minimal risk studies are reviewed every twelve months, and studies that are deemed to be greater than minimal risk are reviewed every six months.

The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:

(1) Involvement of vulnerable populations;

(2) Research conducted internationally;
(3) Use of waiver of informed consent procedures, (e.g. surrogate consent);
(4) Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of adverse events;
(5) Previous Administrative Holds or Suspensions of the research due to compliance, record-keeping or other concerns; and/or
(6) Recommendations from institution.

The IRB has the authority to observe, or have a third party observe, the informed consent process of research it has approved, and to verify that the study is being conducted as required by the IRB and within HCA Midwest Division policies and procedures and site-specific procedures, as appropriate. IRB staff or members may perform site visits or use another party, either affiliated or not with the institution, to verify information in the study application, or in any interim or continuing review submissions.

The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:
(1) Protocols randomly selected by the IRB office;
(2) Complex protocols involving unusual levels or types of risks to participants;
(3) Protocols conducted by PIs who previously have failed to comply with Federal regulations or the requirements or determinations of the IRB; and/or
(4) Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in the initial or continuing review reports or from other sources.

3. Minutes

Minutes, in sufficient detail to reflect the names of the committee members that are present, the action of the committee on each protocol on the agenda, all restrictions, conditions, modifications or additional information requested for each protocol, major issues discussed, and the rationale for each disapproval, will be taken at all IRB meetings. At the convened meeting each submission is discussed and a vote is taken. The IRB minutes will be written by the Administrator and approved by the IRB Chairperson and IRB members at the next convened IRB meeting. The IRB Chairperson will inform the Principal investigator in writing of the decision of the Board, within ten business days of the meeting. If changes are recommended by the board, the IRB Chairperson will communicate these in writing to the Principal investigator.

4. Principal investigator Responses

If a response from a Principal investigator to an IRB letter requesting additional information is not received within three months, the Principal investigator will be sent a notice stating that the protocol application has been administratively withdrawn from consideration. Once it has been administratively withdrawn due to lack of response, the review may be continued only upon receipt of a formal letter requesting reactivation and addressing the concerns raised in the initial review. The new material will then be reviewed by the full Board at the next committee meeting.

Adverse decisions may be appealed by re-review of the proposal. Appeals will be heard only when the proposal has been revised and/or provides additional information.

5. Responsibility

IRB Administrators are responsible for ensuring that IRB reviewers have the tools they need to complete their research reviews. IRB Reviewers are responsible for conducting a thorough review and making all appropriate approval recommendations for consideration by the IRB.

6. Applicable Regulations And Guidelines

45 CFR 46.111
21 CFR 56.108, 56.111

F. IRB AUTHORIZATION AGREEMENTS

1. Policy

The IRB may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort as allowed and upon entering into an IRB Authorization Agreement as provided for by OHRP.

Non-Local IRB
Research may be reviewed by an IRB not located where the research is being performed – *i.e.*, by a non-local IRB. In such situations, the non-local IRB assumes the responsibility for the oversight and continuing review, and the principal investigator (PI) and the facility are responsible for the conduct of the study.

With the use of outside non-local IRBs, a written IRB Agreement must be in place and must include the following:

1. The role and responsibilities of the non-local IRB;
2. An agreement that the entities will comply with relevant federal regulations;
3. A written agreement between the performance site where the research is to be conducted and the non-local IRB or its institution;
4. Language confirming the IRB's responsibility for the oversight of the research.
5. The non-local IRB must copy the facility's designee on all correspondence to the Investigator, specifically letters documenting initial review with dates of approval, continuing review with dates of approval, issues requiring corrective action plans and investigator non-compliance.

Non-local IRBs are held to the same requirements as an institutional IRB. Therefore, they must have adequate knowledge of the community attitudes, information on conditions surrounding the conduct of research and the continuing status of the research to assure compliance with relevant regulations.

Knowledge by the non-local IRB of the community from which subjects are drawn is very important. This assists in safeguarding the rights and welfare of the subjects and that the consent process is appropriate for the subject population of the local community. The IRB should also be sensitive to the local community attitudes and laws regarding research. The capabilities of a non-local IRB to fulfill this requirement must be carefully considered by the institution prior to entering into an IRB Agreement with of this type of an IRB. Non-local IRB meeting documentation should clearly state how community attitudes were obtained and that they were considered with each review, initial and continuing.

Cooperative Research

A single IRB may provide review for several participating institutions. The respective responsibilities of the IRB and institution should be agreed upon in writing by each party. The responsibilities may vary from institution to institution depending on the scope and capabilities of each entity.

Multi-Institutional IRB

Facilities may cooperate to form a multi-institutional IRB that serves a community, hospital system or county and oversees research in all HCA-owned facilities party to the IRB Agreement. This IRB carries out the IRB responsibilities for all HCA-owned institutions and eliminates the individual facilities from having to maintain their own IRBs. The multi-institutional IRB must follow all regulations and requirements that a single-institution IRB would have to follow.

Each institution that participates in a multi-institutional IRB must have a written IRB Agreement with the multi-institutional IRB.

Federally Supported Research and IRB Agreements

IRB Agreements that involve DHHS-supported studies may be subject to DHHS approval through OHRP. Copies of the agreements must be forwarded to all parties to ensure compliance with regulation

2. Responsibility

When HCA Midwest Division's IRB determines that it will rely on another institution's IRB review of a study, or vice versa, HCA Midwest Division's IRB Administrator will create an IRB Authorization Agreement. HCA Midwest Division's Institutional Official, and the other institution's signatory official will sign the document, and copies will be kept on file at both institutions. The IRB Administrator will also amend the FWA accordingly, when appropriate.

3. Applicable Regulations And Guidelines

45 CFR 46.103

G. COLLABORATING INDIVIDUAL INVESTIGATOR AGREEMENTS

1. Policy

The IRB may extend, for one or more research protocols, the applicability of its FWA to cover two types of collaborating individuals: collaborating independent investigators and collaborating institutional investigators.

OHRP notes that some human subject's research conducted by an assured institution may involve the following two types of collaborating individual s:

1. A collaborating independent Principal investigator is:
   a. not otherwise an employee or agent of HCA Midwest Division,
   b. conducting collaborative research activities outside the facilities of HCA Midwest Division, and
   c. not acting as an employee of any institution with respect to his/her involvement in the research being conducted by HCA Midwest Division.

2. A collaborating institutional Principal investigator is:

a. not otherwise an employee or agent of HCA Midwest Division,
b. conducting collaborative research activities outside the facilities of HCA Midwest Division,
c. acting as an employee or agent of a non-assured institution with respect to his/her involvement in the research being conducted by HCA Midwest Division, and
d. employed by, or acting as an agent of, a non-assured institution that does not routinely conduct human subject's research.

HCA Midwest Division will extend its FWA to cover a collaborating independent or institutional investigator provided that all of the following conditions are satisfied:

1. The principal investigator at HCA Midwest Division directs and appropriately supervises all of the collaborative research activities to be performed by the collaborating individual Principal investigator outside HCA Midwest Division.
2. The extension of the coverage of the FWA is put in place by use of an appropriate written agreement, such as the sample Individual Investigator Agreement, for each collaborating individual investigator who will be engaged in the research being conducted by the assured institution. HCA Midwest Division will maintain the Individual Investigator Agreement, or other written agreement used by the assured institution, on file and provides copies to OHRP upon request.
3. For collaborating institutional investigators, the appropriate authorities at the non-assured institution state in writing that the conduct of the research is permitted at their institution.
4. HCA Midwest Division and the responsible IRB designated under the FWA approve the extension of the assurance through either the Individual Investigator Agreement or other written agreement used by HCA Midwest Division.
5. The following documents are made available to the collaborating individual investigator: (a) The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects or Research; (b) the HHS regulations for the protection of human subjects at 45 CFR part 46 and the FDA regulations at 21 CFR 50, 56, 312, and 812, when appropriate; (c) the FWA and applicable Terms of the FWA for the assured institution; and (d) the relevant institutional policies and procedures for the protection of human subjects of HCA Midwest Division.
6. The collaborating individual investigator understands and accepts the responsibility to comply with the standards and requirements stipulated in the documents referenced in the preceding paragraph and to protect the rights and welfare of human subjects involved in research conducted under the Individual Investigator Agreement or other written agreement used by HCA Midwest Division.
7. The collaborating individual investigator agrees to comply with all other applicable federal, international, state, and local laws, regulations, and policies that may provide additional protections for human subjects participating in research conducted under the Individual Investigator Agreement or other written agreement used by HCA Midwest Division.
8. The collaborating individual investigator agrees to abide by all determinations of HCA Midwest Division's IRB and agrees to accept the final authority and decisions of the IRB, including but not limited to directives to terminate participation in designated research activities conducted under the Individual Investigator Agreement or other written agreement used by HCA Midwest Division.
9. The collaborating individual investigator agrees to complete any educational training required by HCA Midwest Division and/or the IRB prior to initiating research covered under the Individual Investigator Agreement or other written agreement used by HCA Midwest Division.
10. The collaborating individual investigator agrees not to enroll subjects in research under the Individual Investigator Agreement or other agreement used by the assured institution, prior to the research being reviewed and approved by the IRB.
11. The collaborating individual investigator agrees to report promptly to the IRB/IEC any

proposed changes in the research conducted under the Individual Investigator Agreement or other agreement used by HCA Midwest Division. The collaborating institutional investigator agrees not to initiate changes in the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.

12. The collaborating individual investigator agrees to report immediately to the IRB any unanticipated problems involving risks to subjects or others in research covered under the Individual Investigator Agreement or other agreement used by HCA Midwest Division.
13. The collaborating individual investigator, when responsible for enrolling subjects, agrees to obtain, document, and maintain records of informed consent for each such subject or each subject's legally authorized representative as required under HHS regulations at 45 CFR part 46 and stipulated by the IRB.
14. The collaborating individual investigator acknowledges and agrees to cooperate with the IRB's in its initial and continuing review, record keeping, reporting, and certification for the research covered by the Individual Investigator Agreement, or other agreement used by HCA Midwest Division. The collaborating institutional investigator agrees to provide all information requested by the IRB in a timely fashion.

2. Responsibility

When HCA Midwest Division decides to extend, for one or more research protocols, the applicability of its FWA to cover collaborating individual investigators HCA Midwest Division's IRB Administrator will create an Individual Investigator Agreement. The Signatory Official, and the individual investigator will sign the document, and copies will be kept on file at both institutions.

3. Applicable Regulations And Guidelines

45 CFR 46.103 (a)
45 CFR 46.103 (b)
OHRP Guidance on Extension of an FWA to Cover Collaborating Individual Investigators and Introduction of the Individual Investigator Agreement, January 31, 2005

H. Waiver of Authorizations

1. Policy

The IRB may not authorize the use or disclosure of protected health information for research purposes unless at least one of the following exceptions applies:

a. Reviews Preparatory to Research. The HIPAA Privacy Rule allows researchers to access protected health information for reviews preparatory to research if certain representations are made. However, at HCA Midwest Division all human subjects research, including screening of records and recruitment of subjects must be approved by an IRB. Because the IRB reviews and approves all screening of records and recruitment of subjects in the IRB's protocol approval process, HIPAA's concept of "reviews preparatory to research" is incorporated into the IRB review process. This happens in one of two ways. First, if subjects will be asked for their authorizations to review files and/or be recruited, such authorization obviates the need for any representations from the PI for a review preparatory to research. Second, if subjects will not be asked for their authorizations to review files and/or be recruited, the IRB's

approval of the protocol will include a waiver of authorization which also obviates the need for any representations from the PI for a review preparatory to research.

However, if a review preparatory to research activity would be an exempt activity under regulations relating to human subjects research (45 CFR § 46.101(b)) but involves the use of protected health information as defined under HIPAA, then the IRB will not approve the review preparatory to research as part of a protocol. In such case the researcher would need to make the following HIPAA representations:

- the use or disclosure is sought solely to prepare a research protocol or for similar purposes preparatory to research;
- no researcher will remove any protected health information from HCA Midwest Division 'x premises in the course of the review; and
- the protected health information for which use or access is sought is necessary for the research purposes.

The IRB must approve the activity based on the representations of the PI

During the preparatory review, those granted access may record information only in a form that is "de-identified."

b. Research on the Protected Health Information of a Decedent. Under the Common Rule and FDA requirements, the IRB does not review research on data relating to decedents. However, under the HIPAA Privacy Rule, access to identified information on decedents requires that certain representations be made by the researcher. The IRB has assumed the role of assuring that those representations are made. The IRB may permit the use and disclosure of the protected health information of a decedent for research purposes if the PI submits to the IRB representations that the use or disclosure is sought solely for research on the protected health information of a decedent (e.g., researchers may not request a decedent's medical history to obtain health information about a decedent's living relative) and that the information for which use or disclosure is sought is necessary for the research purposes. The PI must provide, at the IRB's request, documentation of the death of any individuals about whom information is sought. HIPAA IRB Form 5 is the certification form that must be signed by researchers seeking to engage in research on the protected health information of a decedent.

c. Informed Consents Obtained or Waivers of Informed Consent Approved Prior to April 14, 2003. The IRB may approve the use or disclosure of protected health information for a specific research project provided that one of the three following requirements is met:

- Express Legal Permission For Use And Disclosure Of Protected Health Information. If, prior to April 14, 2003, the researcher obtained express legal permission from the individual that specifically authorizes a use or disclosure of protected health information for purposes of the research project, the IRB may permit the use or disclosure for purposes of that project. However, any restrictions on the use and disclosure of health information provided in the express legal permission must be honored.
- General Informed Consent. If, prior to April 14, 2003, the researcher obtained the individual's informed consent to participate in a specific research project, the IRB may permit a use or disclosure of protected health information for purposes of that project even though the informed consent does not specifically authorize the use or disclosure of protected health information for purposes of the research project. However, any

restrictions on the use and disclosure of health information stated in the IRB approved informed consent document must be honored.

- Waiver Of Informed Consent. If, prior to April 14, 2003, the researcher obtained an IRB waiver of the informed consent requirement (in accordance with the Common Rule) for a specific research project, the IRB may permit a use or disclosure of the individual's protected health information for purposes of that project. However, if the researcher obtains an individual subject's informed consent at any time on or after April 14, 2003, the researcher also will be required to obtain the individual's Research Authorization (as provided in this policy) at that time.

d. Completely De-identified Information**.** The IRB may allow completely de-identified information to be used and disclosed for research purposes without restriction. Information may be considered completely de-identified only when either (1) a qualified statistician documents his or her determination that the risk of identification is very small (see Appendix A of this policy), or (2) the information meets the safe harbor requirements. If the IRB has any doubts as to whether protected health information has been completely de-identified within the meaning of this policy, the information should be treated as though it were not completely de-identified and neither used nor disclosed for research purposes unless it meets the criteria for another exception.

e. Limited Data Set**.** The IRB may allow the use and disclosure for research purposes of a limited data set including a partially de-identified subset of the individual's protected health information, provided that the person using or receiving the information has signed a Data Use Agreement through which he or she agrees to protect the privacy of the information received. Appendix B of this policy provides more information about the identifiers that must be removed from an individual's protected health information in order to create a limited data set.

f. Subject Authorization For Research**.** The IRB may allow the use and disclosure of protected health information pursuant to a completed and signed privacy authorization form. This may be a separate form or combined with the informed consent. Permissible uses and disclosures are limited to those described in the authorization.

The authorization must be completed by the PI. It is the responsibility of the Principal investigator to ensure that the authorization form covers the uses and disclosures necessary for the research study.

After preparing the form, the PI must submit the form to the IRB for approval. The IRB must stamp its approval on the form before any protected health information obtained by the PI may be used or disclosed for research purposes.

When obtaining an authorization, an individual's ability to receive research-related treatment as part of a research study is conditioned upon the individual's agreement to sign the authorization form. However, in presenting the authorization form to prospective subjects, researchers must not suggest that failure to sign the form will limit access to any treatment that may be available outside the study. Any questions about the availability of treatment outside the study should be referred to the prospective subject's physician(s).

g. IRB Approval of Waiver**.** The IRB may allow the use and disclosure of protected health information for research purposes if the IRB grants a partial or total waiver of the

authorization requirement. If the IRB or Privacy Board grants only a partial waiver – that is, if it modifies or waives only some elements of the privacy authorization form or process – the IRB must condition the use and/or disclosure of any protected health information for research purposes on compliance with any authorization requirements not waived and as modified. .

The IRB must document the waiver. The documentation must include at least:

- the name of the IRB;
- the date on which the waiver was approved;
- the signature of the Chair of the IRB, or other member designated by the chair;
- a statement that the IRB has determined that the waiver satisfies the required criteria;
- a brief description of the protected health information that the IRB has determined is necessary for research purposes; and

- a statement that the waiver has been reviewed and approved under either normal or expedited review procedures and that all applicable procedures were followed.

2. Documentation

The IRB must retain any writings or documentation required by this policy for six years from the date of the creation of the information or the date when it last was in effect, whichever is later.

3. Review Procedures.

Review proposed research at convened meetings at which a majority of the Privacy Board members are present, including at least one member who is not (1) affiliated with HCA Midwest Division , (2) affiliated with any entity conducting or sponsoring the research, or (3) related to any person who is affiliated with either HCA Midwest Division or an entity conducting or sponsoring the research; or approve the waiver pursuant to an expedited review procedure, in which case the review and approval of the waiver of authorization may be carried out by the chair of the Privacy Board, or by one or more members of the Privacy Board as designated by the chair.

VIII. INITIAL REVIEW CONSIDERATIONS

A. POLICY

All research proposals that intend to enroll human subjects must meet certain criteria before study related procedures can be initiated. The criteria are based on the principles of justice, beneficence and autonomy as discussed in the Belmont Report and are specified below. This policy applies to all initial reviews, whether they are conducted via expedited review or at a convened meeting.

B. MINIMAL CRITERIA FOR APPROVAL OF RESEARCH

1. In order for a research project to be approved, the IRB must find that:

a. Risks to subjects are minimized:
   - By using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
   - Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.

2. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from 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.

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

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by appropriate local, state and federal regulations.

5. Informed consent will be appropriately documented as required by local, state and federal regulations.

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

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

8. When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence or for subjects found at international sites, additional safeguards have been included in the study and in the IRB review process, to protect the rights and welfare of these subjects.

C. STUDY POPULATION

The prospective study population must be appropriate with respect to the nature and goals of the research. The IRB will examine carefully the characteristics of the subject population. Factors such as the required number of subjects, age range, sex, ethnic background and health status will be considered. The utilization of any vulnerable classes of subjects, such as fetuses, prisoners, children, and mentally incompetent persons, must be clearly justified. Although the use of vulnerable persons as subjects is not prohibited by any regulations or ethical codes, justification for their involvement in research generally becomes more difficult as the degree of risk and vulnerability increases.

Naturally, there are exceptions to the principle of "equitable selection of subjects." For instance, research involving the study of a disease which is prevalent in only one ethnic or racial group (e.g.,

sickle cell anemia and Tay - Sachs disease) would not require the application of this principle.

In past years, the standard has been to exclude populations from participation in research activities when there is no evidence of safety in those populations. For example, pregnant women have been largely excluded from research because there is seldom safety data available for pregnant women and fetuses.

Every blanket exclusion of particular populations from potentially beneficial studies be justified based on data from the literature on the drug/device/procedure being studied. It is important to note that the absence of data confirming safety is not equivalent to the presence of data confirming risk.

D. SUBJECT RECRUITMENT

The IRB will review the method of prospective subject identification and recruitment in order to be assured that it is ethically and legally acceptable. Advertisements used to recruit subjects are considered an extension of the recruitment and informed consent processes and, therefore, must be reviewed and approved by the IRB.

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While a Principal investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of or in preparation for the research, it is part of the research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

E. EXPERIMENTAL DESIGN

While the IRB is not charged by Federal regulation with the responsibility of reviewing protocols for scientific merit, issues related to the adequacy of the scientific design often emerge during the review. Such issues as inclusion of adequate and appropriate controls, adequacy of sample size, and appropriateness of experimental endpoints may be raised in the review. The IRB will make a judgment on the validity of the study design as part of its assessment of the risk/benefit ratio, because no risk to subjects can be justified ethically if the study design is flawed to the degree that no useful information is likely to be forthcoming.

In reviewing any protocol, the IRB should be provided with complete information regarding experimental design and the scientific rationale (including the results of previous animal and human studies) underlying the proposed research, and the statistical basis for the structure of the investigation.

Deception of Research Subjects

It should be noted that while the IRB accepts the need for certain types of research to employ strategies that include either deception and/or withholding of information, use of such strategies must be fully justified. In general, deception is not acceptable if in the judgment of the IRB the subject would have declined to participate had they been informed of the true purpose of the research. For example, investigational drug studies, which require a "washout period", during which the subject is given a placebo rather than his/her regularly prescribed drug, must generally be so informed.

When evaluating the use of deception in research, the IRB will discuss the following issues:
(1) Validity of the research,
(2) Alternative methodologies,
(3) The characteristics, values, and morals of the experimental sample,
(4) Potential harm,
(5) Privacy and confidentiality, and
(6) Informed consent.
   a. Although subjects may not be fully informed, they should be informed of as much as possible without threatening the ability of the researcher to test the true hypothesis of the study.
   b. HCA Midwest Division's recommendation is that the consent form should:
      1. Never be used as part of the deception and thus should not include anything that is untrue, and
      2. Reveal as much as possible to the participant regarding the procedures in the study.
      3. The consent form does not need to detail specific elements of the study if this will eliminate the capability of the study to inform the process under investigation.

F. POTENTIAL RISKS

Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. This requirement is clearly stated in all codes of research ethics, and is central to the policies of HCA Midwest Division and existing federal regulations. One of the major responsibilities of the IRB, therefore, is to assess the risks and benefits of proposed research.

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

In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with therapies subjects would undergo even if not participating in research, will be considered. For example, if the research is designed to measure the behavioral results of physical interventions performed for therapeutic reasons (e.g., effects on memory of brain surgery performed for the relief of epilepsy), then only the risks presented by the memory tests will be considered when the IRB performs its risk/benefit analysis. It is possible for the risks of the research to be minimal even when the therapeutic procedure presents more than minimal risk. HCA Midwest Division's IRB will recognize, however, that distinguishing therapeutic from research activities can sometimes require very fine line drawing. Before eliminating an activity from consideration in its risk/benefit analysis, the IRB will be certain that the activity truly constitutes

therapy and not research.

Minimal Risk vs. Greater Than Minimal Risk

Minimal risk is broadly defined as the probability of and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life [of the proposed study subjects -- may be broadened if approved by the IRB] or during the performance of routine physical or psychological examinations or tests (e.g., collection of urine, collection of sweat, weighing, pulse measurement, voice recordings, electrocardiography).

The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. Minimal risk for prisoners, "is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.**"**

Once the risks have been identified, the IRB will assess whether the research presents greater than minimal risk. The IRB may use the expedited review process for proposals, which meet certain conditions (the research must present no more than minimal risk and the involvement of human subjects must fall into one or more categories as outlined, in the Expedited Review section).
On average, if the IRB determines that a research study is minimal risk, then it will be reviewed annually, and if the IRB determines that a research study is greater than minimal risk, then it will be reviewed every six months. The approval letter that is sent to the Principal investigator following the IRB approval of the study will note the risk classification and how often it will be reviewed by the IRB.

In research presenting more than minimal risk, potential subjects must be informed of the availability of medical treatment and compensation in the case of research-related injury, including who will pay for the treatment and the availability of other financial compensation.

Determination that Risks are Minimized

Risks, even when unavoidable, can be reduced or managed. Precautions, safeguards, and alternatives can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration. The IRB is responsible for assuring that risks are minimized to the extent possible.

The IRB will analyze the beneficial and harmful effects anticipated in the research, as well as the effects of any treatments that might be administered in ordinary practice, and those associated with receiving no treatment at all. In addition, it will consider whether potentially harmful effects can be adequately detected, prevented, or treated. The risks and complications of any underlying disease that may be present must also be assessed.

G. POTENTIAL BENEFITS

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

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

H. RISK-BENEFIT ANALYSIS

Once the potential risks and benefits are identified, the IRB will examine the relationship of the risks to the benefits. Risks and benefits cannot be considered parallel constructs and, therefore, no formula is applicable. The various ethical codes and regulations, however, require a favorable balance between harm and benefit.

In research that has no likelihood or intent of producing a diagnostic, preventive or therapeutic benefit to the subject (non-therapeutic research), the potential risk to the subject must be outweighed or balanced by the potential benefit to the subject and/or by the potential benefit to society.

In research involving the study of the efficacy of a therapeutic or diagnostic method and the intervention is, therefore, not designed solely to enhance the well-being of the subject who is seeking a health benefit (therapeutic research), the potential risk should be primarily outweighed or balanced by the potential benefit to the subject. In addition, the relationship of the potential benefit to the risk must be at least as favorable to the subject as that presented by alternate standard therapies available to the subject in the non-research context. No subject is allowed to continue participating in a research protocol if therapy of proven superior nature becomes available to the subject.

In research where a standard therapy not part of the research protocol is employed solely for the benefit of the subject along with additional procedures performed solely for research purposes, the potential benefits of the therapy will not be used to justify exposing subjects to the risks associated with the research procedures. Such risks can only be justified in light of the potential benefits of the research procedures. Conversely, only the risks associated with the research procedures will be used in determining the risk-benefit ratio.

I. SUBJECT COMPENSATION

The IRB will review the amount of compensation (monetary as well as other forms), and schedule of all payments in order to be assured that neither are coercive nor present undue influence. Actual/estimated costs, such as for transportation and child care, may be the basis for payments to the study subjects.

J. CONFIDENTIALITY

The IRB will review the methods to be used to reserve confidentiality. If research data with subject identifiers will be made available to persons other than the listed Principal investigators, sponsor or federal agency, the IRB will review the justification for sharing this data and determine acceptability.

Certificates of Confidentiality should be obtained for studies collecting information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to

participants.

Researchers, with a Certificate of Confidentiality are not prevented from the voluntary disclosure of matters such as child abuse, reportable communicable diseases, or subject's threatened violence to self or others. Therefore, if the researcher intends to make any voluntary disclosures, the consent form must specify such disclosure.

Authorization to Use or Disclose PHI

Informed consent must include the following authorization core elements and statements included in this confidentiality section of the informed consent document unless offered in a separate form:

- A description of the PHI to be used or disclosed;
- The name or other specific identification of the person or class or persons authorized to make the requested use or disclosure (*e.g.*, hospital name, physician name);
- The name or other specific identification of the person or class or persons to whom the facility may make the requested use or disclosure (*e.g.*, the researcher);
- A description of the purpose of the requested use or disclosure;
- An expiration date or event (*e.g.*, "end of research study" or "none");
- A statement that the individual has the right to revoke the authorization in writing and the exceptions to this right (*i.e.*, facility has already taken reliance on authorization);
- A statement that if the patient refuses to sign the consent, including the authorization elements, that he/she will not be treated under the research protocol; and
- A statement that the PHI is subject to redisclosure by the recipient and may no longer be protected.

The IRB must ensure that the above listed elements are contained in the informed consent document. Additionally, the IRB must assure that if there are any State/Local specific HIPAA pre-emptions, that the Authorization language is in compliance with both HIPAA and the additional State/Local requirements (*i.e.*, California, Oklahoma).

Denial of Patients Right to Access their Protected Health Information

Informed consent information must describe the extent to which a patient would be temporarily denied access to their protected health information (PHI) created or obtained in the course of research until the research project was completed. This requirement pertains only to research where patient treatment is involved.

K. INFORMED CONSENT

The informed consent form must embody the elements of informed consent contained in the HHS , HIPAA Privacy Standards', and/or FDA regulations. The IRB will review both the consent form and the process of informed consent to ensure its acceptability.

The basic elements of the consent process, as detailed below, include:
(1) Full disclosure of the nature of the research and the subject's participation,
(2) Adequate comprehension on the part of the potential subject, and
(3) The subject's voluntary choice to participate.

In most research activities, an informed consent must be obtained by the Principal investigator or his/her designee from each of the participants; or, in the case of those not able to give consent (e.g., children, mentally retarded), consent must be obtained from their guardians or legal representatives. A copy of the informed consent should be given to the person signing the form. The IRB must

approve all consent documents and copies of such will be kept on file by the IRB.

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

In clear and non-technical language, subjects must be informed of:

(1) The fact that the study is research.
(2) The purposes of the research.
(3) The expected duration of the subject's participation.
(4) The procedures to be followed, whether there will be hospitalization to receive treatments, statements regarding medical procedures that will be performed and whether any are experimental. Include how many treatments will be given, how often and over what period of time.
(5) Any reasonably foreseeable risks or discomforts.
(6) The benefits to the subject or to others, which may reasonably be expected from the research.
(7) Appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.
(8) The extent to which confidentiality of data and privacy of subjects will be maintained.
(9) For research involving more than minimal risk, whether any medical treatments are available if injury occurs or whether there is any compensation for injury, and if so, what they consist of, or where further information may be obtained.
(10) Who to contact for answers to pertinent questions about the research, subjects' rights, and research-related injury to the subject. Include complete phone numbers and contact persons for various categories (about the specific study or about patient rights in general) of information that may become important to the subject at a later date. The contact for research subjects' rights should be the local IRB Chairperson.
(11) The fact that participation is voluntary and that the subject may withdraw his or her consent at any time without penalty or loss of benefits.

The following additional elements of information shall also be provided to each subject, when appropriate:

(1) A statement that the particular treatment or procedure may involve risks to the subject, (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
(2) A statement that there are circumstances under which the subject may be terminated from participation by the Principal investigator without the subject's consent such as when the subject does not follow the given instructions given to them.
(3) A description of additional costs that may result from participation in the research, noting that some insurance carriers may not pay for care that is delivered in a research context.
(4) An explanation of any consequences of a subject's voluntary withdrawal from the research and procedures for orderly termination of participation by the subject to protect the welfare of the subject.
(5) A statement that the subject will be notified of any significant new findings developed during the course of the research which may influence the subject's willingness to continue participation.
(6) Indicate the approximate number of subjects involved in the study.

Other general guidelines to preparing informed consent documents:

(1) The use of the wording "I Understand" is inappropriate since most subjects will not understand the scientific and medical significance of all the statements. Also statements such as "This study has been fully explained to me" or "I fully understand the study" are inappropriate since the subjects cannot certify completeness of disclosure.
(2) Use of the first person can be interpreted as suggestive, may be relied upon as a substitute for sufficient factual information, and can constitute coercive influence over a subject.
(3) Use of scientific jargon and legalese is not appropriate.
(4) No unsubstantiated claims of effectiveness or overly optimistic representations should be included.
(5) Payments to the subjects should accrue as the study progresses and should not be an amount that could be considered coercive. The amount and schedule of payments should be submitted to the IRB for approval.
(6) FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study.
(7) Phrases such as "FDA has given permission" or "FDA has approved" should not be used.
(8) FDA explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative. HHS regulations do not explicitly require consent forms to be dated.
(9) For all research involving test articles regulated by the FDA, informed consent documents must include a statement that the purpose of the study includes evaluation of both the safety and the effectiveness of the test article. The consent form must also include a statement that the FDA has access to the subject's medical records. The recommended consent language for FDA regulated research is:

    "*Because this research involves articles regulated by the Food and Drug Administration (FDA), the FDA may choose to inspect and copy medical or research records that identifies individual subjects."*

(10) When the study subject population includes non-English speaking people, or if the Principal investigator has reason to believe the subject does not fully comprehend English, or if the consent interviews will be conducted in another language other than English, the IRB requires a translated consent document. A non-English speaking subject should receive a copy of the translated document.

10. A person who speaks and understands English, but does not read and write, can enroll by "marking their mark" on the consent document. An impartial witness should attest to the adequacy of the consent process and that the subject voluntarily agrees.

Special issues arise when the subjects participating in research do not speak or read English, and great care must be taken to be sure that the individual understands the information about the study. Whenever possible, documentation should take the form of a written consent document drafted in language understandable to the subject that embodies all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a consent document written in the subject's preferred language. The IRB has the standard consent form on file in all languages provided. If no IRB member is competent to review the translated forms, the IRB considers the advice of a consultant or translating person/organization in approving/disapproving the foreign language consent form.

Alternatively, if an oral presentation of informed consent information is used with subjects who do not speak English (or cannot read), in addition to the requirements described above, (i) the

oral presentation and the short form written document should be in a language readily understandable to the subject; (ii) the English language informed consent document approved by the IRB may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject. When a translator assists the person obtaining consent, the translator may serve as the witness. The IRB must receive all foreign language versions of the short form document and any other translated documents presented to the subjects as a condition of approval. Expedited Review of foreign language versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

Illiterate persons who understand English may have the consent form read to them and make a "mark" on the subject signature line. Signatures of the witness to the consent process and the person conducting the consent interview are required in such situations. The IRB considers illiterate persons as likely to be vulnerable to coercion and undue influence and, therefore, considers whether appropriate additional safeguards are in place when enrollment of such persons is anticipated. The recommended consent language for subjects who cannot read:

The study subject has indicated that he/she is unable to read. This Authorization document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

(11) For research with children, children about the age of 8 or 9 and above should sign assent; full consent is signed by the parent or legal guardian (please see the section on IRB Special Review Considerations – Research Involving Children, for more information regarding assent and consent for this population).

(12) While most individuals assume that therapists and teachers act in the patient's or students best interest, evidence has indicated that this assumption persists even if the subjects are told that the activity is research and will have no direct benefit for them. Therefore, special care must be taken in these settings to ensure that the potential subjects understand the nature of the research.

No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the Principal investigator, the sponsor, the institution, or its agents from liability for negligence (45 CFR 46.116).

Documentation of Informed Consent

Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative, and the person obtaining consent. A copy shall be given to the person signing the form.

The consent form may be either of the following:

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

(2) A short form written consent document stating that the required elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form

itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

Subjects who do not speak English: Where informed consent is documented using this short form procedure for non-English speaking subjects, the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written informed consent document should be in a language understandable to the subject; (ii) the approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the convened full IRB has already approved the protocol, the full English language informed consent document, and the English version of the short form document.

With appropriate justification, the IRB may waive the documentation requirement for informed consent (45 CFR 46.117). Principal investigators contemplating such a request should discuss this with the IRB staff before submitting their protocol for approval.

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

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (note that FDA does NOT provide that an IRB may waive the requirement for signed consent when the principal risk is a breach of confidentiality because FDA does not regulate studies, which would fall into that category of research); or
(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

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

Informed Consent Alterations and Waivers

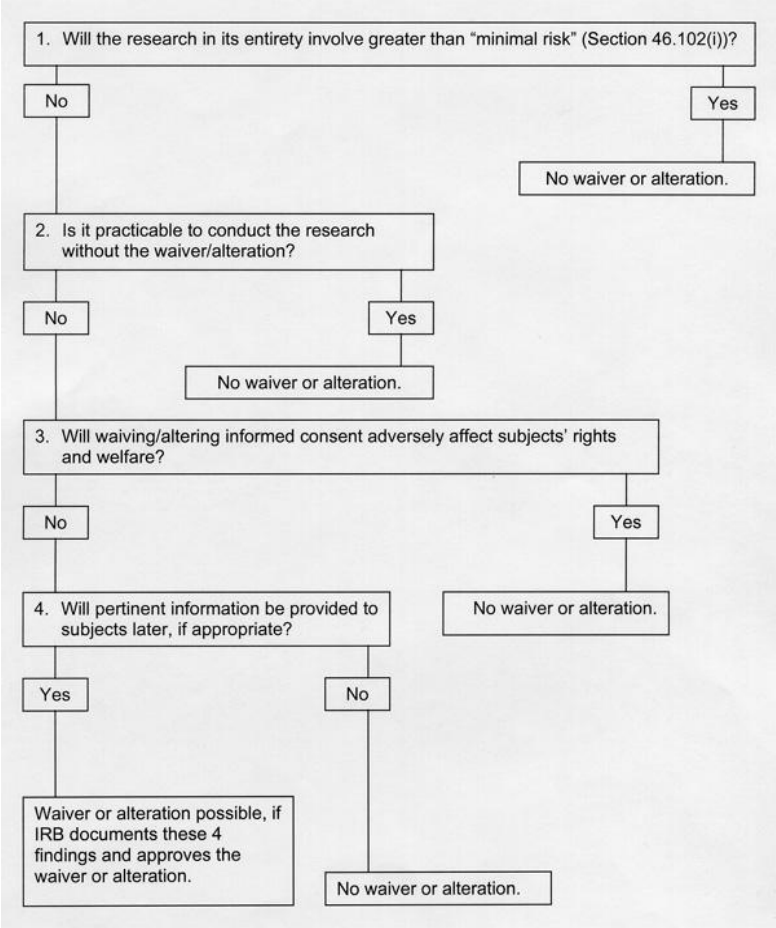
With appropriate justification, the IRB may waive the requirement for informed consent (45 CFR 46.116 (d)). Principal investigators contemplating such a request should discuss this with the IRB staff before submitting their protocol for approval.

The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
(3) The research could not practicably be carried out without the waiver or alteration; and
(4) Whenever appropriate, the subjects will be provided with additional pertinent information

after participation.

The following OHRP Decision Chart will be used to help determine if the IRB can employ 45 CFR 46.116(d) to waive informed consent or alter informed consent requirements:



FDA provides for an exception from the informed consent requirements only in emergency situations. The provision is based on the Medical Device Amendments of 1976, but may be used in investigations involving drugs, devices, and other FDA regulated products in situations described in 20 CFR 50.23. FDA has no other provision for waiving or altering elements of informed consent under certain conditions, because the types of studies, which would qualify for such waivers are either not regulated by FDA.

FDA Exception from Informed Consent Requirement: Emergency Use

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

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article.
(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject.

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

FDA Exception From Informed Consent Requirement: Emergency Research

For FDA regulated studies, the informed consent requirements can only be waived if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following for emergency research:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:
   a. The subjects will not be able to give their informed consent as a result of their medical condition;
   b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
   c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:
   a. Subjects are facing a life-threatening situation that necessitates intervention
   b. Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
   c. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the Principal investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The Principal investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent

document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
   a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
   b. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
   c. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
   d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
   e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the Principal investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The Principal investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The Principal investigator (and ultimately the IRB) is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

Protocols involving an exception to the informed consent requirement must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the above-mentioned criteria or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the clinical Principal investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA.

Cognitively Impaired Subjects

Studies involving subjects who are decisionally impaired may take place over extended periods. The IRB should consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. The IRB may require that Principal investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB should consider whether, and when, it should require a reassessment of decision-making capacity.

Use of Facsimile or Mail to Document Informed Consent

In rare circumstances, depending upon the design of a study, the IRB may approve a process that allows the informed consent document to be delivered by mail or facsimile to the potential subject or the potential subject's legally authorized representative and to conduct the consent interview by telephone when the subject or the legally authorized representative can read the consent document as it is discussed. The consent document must be returned to the Principal investigator with the signature of the subject or subject's legally authorized representative, by mail or facsimile, before any research procedures may be implemented. All other applicable conditions for documentation of informed consent must also be met when using this procedure.

Monitoring of the consent forms and process by the IRB:

For each study, the IRB must develop a mechanism to be assured there is evidence that each prospective subject or authorized representative received informed consent through the appropriate predetermined process and the current IRB-approved consent document is utilized.

L. AUDIOTAPING, VIDEOTAPING, AND STILL PHOTOGRAPHY

Principal investigators' plans for recording data should receive prospective IRB review and be included in the informed consent process. Plans to destroy, share, or archive the recordings should also be discussed with the IRB and with study participants. If a Principal investigator chooses to archive recordings but obscure the identities of participants in publication, then plans for protecting the confidentiality of the original study records must also be addressed.

Occasionally, although Principal investigators prefer to record or photograph participants, they state that they could carry out their research without such recordings. In these cases, participants should be provided with an opportunity to consent or decline to consent to recordings. This may be assured by providing separate consent forms, one to participate in the research, and one to participate in the recordings.

M. REVIEW OF PRINCIPAL INVESTIGATOR QUALIFICATIONS

The IRB will review Principal investigator qualifications and must be assured that:

(1) The Principal investigator has the appropriate qualifications and licensure to carry out the procedures involving human subjects with an acceptable degree of risk, and
(2) The Principal investigator has adequate facilities to conduct the research with an acceptable degree of risk.

N. STATE LAWS

Every state has its own statutes, regulations, and case law that may impose requirements on the research process that add to or are different from what federal law requires. Although some federal laws in essence "overrule" conflicting state laws, this is generally not the case with state laws relating to the research process. These laws vary considerably from state to state.

The IRB will review the following, to make sure that the protocol is consistent with state regulations:
(1) Age of consent
(2) Capacity to consent/legally authorized representative
(3) Children's assent
(4) Informed consent
(5) Genetic research
(6) Confidentiality of medical records
(7) HIV/STD reporting requirements
(8) Laws about referral fees and recruitment methods
(9) Laws governing clinical research, and investigational drugs
(10)Laws about vulnerable patients
(11)Laws about medical practice and delegation of authority to perform procedures.

See the Appendices for specific state rules for research being performed in California and Maryland.

O. DETERMINATIONS

After the IRB has discussed the protocol, consent form, and supporting documents, the IRB will determine if the requirements of 45 CFR 46.111 (21 CFR 56.111) (*see #2 of this section for a detailed list of the requirements*) have been satisfied. If the requirements have not been satisfied, the IRB will not approve the study. If the requirements have been satisfied, the IRB will discuss whether the study should be approved or not.

Conditional Approvals:

For minor clarifications or modifications, the IRB may provide Conditional Approval to the investigator accompanied by specific instructions provided:
1) the investigator is informed of the specific and unambiguous changes required for the research to be approved (*i.e.*, "meet all Federal Requirements in the Informed Consent Form" is not specific enough to meet this criteria where "add 'A minor skin rash that lasts 3-7 days has been noted in approximately 10% of subjects' in the risk section and change 'if you withdraw from the study, it will not affect your care at this institution' to 'if you withdraw from the study before it is over, you do not lose any rights or benefits to which you are otherwise entitled'" details the specifics required by the IRB);

2) the investigator is informed that they cannot begin this research until the changes have been made; and

3) the IRB receives evidence that the changes were made prior to the investigator conducting the research.

Only when the IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

If and when the IRB requests substantive clarifications or modifications regarding the research, the approval of the proposed research should not be given conditionally but must be **deferred**, pending subsequent review of responsive material.

If the IRB granted Conditional Approval, the time runs from the date of the convened meeting or Expedited Review and not when the investigator furnishes the required changes. For protocols that were deferred and later approved at a subsequent meeting, time runs from the date that approval was actually given and not the first meeting the protocol was presented and deferred.

Once the IRB has voted to approve a study, the IRB will make a risk determination for the study, and then determine the review period. Studies are reviewed at periods appropriate to the degree of risk subjects are exposed to due to their participation in the study, but at least annually. The IRB determines a review interval for the research as appropriate to the degree of risk, but not greater than one year from the last date of IRB approval. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of the research occurs on or before the date when IRB approval expires. The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:

(1) Involvement of vulnerable populations;
(2) Research conducted internationally;
(3) Use of waiver of informed consent procedures, (e.g. surrogate consent);
(4) Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of adverse events;
(5) Previous Administrative Holds or Suspensions of the research due to compliance, record-keeping or other concerns; and/or
(6) Recommendations from institution.

On occasion, the IRB may also determine that the PI should submit a periodic report prior to the date of the continuing review. Examples of these types of reports include an update regarding recruitment, an update regarding a new procedure, an update after the first subject has been medicated, etc. These types of reports will be requested when the IRB feels that it is necessary to be updated on specific information within a certain time frame, however, it does not deem it necessary to conduct a complete continuing review at this time. When this type of periodic report is requested, it will be stated in the approval letter, along with the due date of the report.

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

(1) Protocols randomly selected by the IRB office;
(2) Complex protocols involving unusual levels or types of risks to participants;
(3) Protocols conducted by PIs who previously have failed to comply with Federal regulations or the requirements or determinations of the IRB; and/or
(4) Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.

If Subparts B, C, or D is applicable to the research, the IRB will review the research under the appropriate subpart and determine if the requirements have been satisfied.

P. RESPONSIBILITY

IRB Administrators are responsible for ensuring that IRB reviewers have the tools they need to complete their research reviews. IRB Reviewers are responsible for conducting a thorough review and making all appropriate approval recommendations for consideration by the IRB.

Q. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.111
21 CFR 56.108, 56.111

IX. REVIEWS REQUIRING SPECIAL CONSIDERATIONS

A. VULNERABLE POPULATIONS

1. Policy

a. Not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Some persons are in need of extensive protection, even to the point of excluding them from activities that may harm them. Other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. Indeed, some types of research may, in and of themselves, create a vulnerable group – that is, the subjects lose their autonomy or are exposed to unknown risks. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations. IRB will have appropriate subject advocate representatives present at the meeting.

b. Potentially vulnerable groups may include:
   1. Prisoners
   2. Children
   3. Pregnant women and fetuses
   4. Decisionally impaired, such as mentally limited, substance abusers
   5. Other vulnerable groups

2. Prisoners

Inasmuch as prisoners may be under constraints because of their incarceration, which could affect their ability to make a truly voluntary and uncorked decision whether or not to participate as subjects in research, DHHS regulations at 45 CFR 46, subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners as subjects.

The provisions of subpart C apply to any research conducted or supported by HCA Midwest Division in which prisoners are subjects. This includes research that involves individuals who are prisoners at the time of enrollment in the research or individuals who become prisoners after they

become enrolled in the research. In the latter situation, it is unlikely that review of the research and the consent document contemplated the constraints imposed by incarceration.

"Prisoner" is defined by HHS regulations at 45 CFR part 46.303(c) as "any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing."

When the IRB reviews a protocol involving prisoners as subjects, the composition of the IRB will satisfy the following requirements of HHS regulations at 45 CFR 46.304(a) and (b):

ii. A majority of the IRB (exclusive of prisoner members) will have no association with the prison(s) involved, apart from their membership on the IRB.
iii. At least one member of the IRB will be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

HCA Midwest Division's IRB has at least one prisoner representative who has a close working knowledge, understanding, and appreciation of prison conditions from the perspective of the prisoner. The prisoner representative will be present at every IRB meeting, in which a protocol involving prisoners as subjects is reviewed, for all types of review of the protocol (including initial review, continuing review, review of protocol amendments, and review of reports of unanticipated problems involving risks to subjects). The curriculum vitae of the prisoner representative, serving on the IRB is on file in the IRB office and with OHRP.

At HCA Midwest Division, initial review of research involving prisoners will only be performed at convened IRB meetings. Only continuing review of research involving prisoners under the following conditions may be reviewed via an expedited review procedure:
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.

Research involving prisoners may not be exempted.

Permitted Research Involving Prisoners

The definition of minimal risk for prisoner research at 45 CFR 46.303(d) differs from the definition of minimal risk for other research, contained in 45 CFR 46, subpart A, 45 CFR 46.102(i). Minimal risk for prisoners, "is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.**"**

The categories of permissible research involving prisoners are the following:

(1) 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 (i);

(2) 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 (ii);

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

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

IRB Review of Research Involving Prisoners

When the IRB is reviewing a protocol in which a prisoner is a subject, the IRB will make, in addition to other requirements under 45 CFR 46, subpart A, seven additional findings under 45 CFR 46.305(a), as follows:

(1) The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2) [noted above];

(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;

(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 participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

These seven additional findings made by the IRB will be documented in the minutes of the IRB meeting, in which the protocol was reviewed as a prison study.

Approval of Research Involving Prisoners

For research conducted or supported by HCA Midwest Division to involve prisoners, two actions must occur:

(1) HCA Midwest Division must certify to the Secretary (through OHRP) that the IRB has reviewed and approved the research under 45 CFR 46.305; and
(2) The Secretary (through OHRP) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

After a protocol involving prisoners as subjects has been approved by the IRB, the IRB Administrator will send a certification letter that the IRB has made the seven additional findings required under 45 CFR 46.305(a), along with a copy of the research protocol, informed consent document, Application for Study Review, and Application for Research Involving Prisoners to OHRP.

Research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to HCA Midwest Division on behalf of the Secretary under 45 CFR 46.306(a)(2).

Once an approval letter is received from OHRP in the IRB office, a copy of the letter and a non-contingent approval letter from the IRB will be forwarded to the Principal investigator. At this point, and this point only, may a Principal investigator begin to recruit prisoners as subjects.

3. Children

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. Research that is contrary to the rights and welfare of child-subjects is prohibited. The IRB must take great care in approving research where the child is suffering from a life-threatening illness with little real chance of therapeutic benefit from the research. The IRB must also be cautious in allowing parents to overrule a child’s dissent where experimental therapy has little or no reasonable expectation of benefit.

Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted", 45 CFR 46.402(a).

Analysis of Probable Risks, Possible Benefits, and Associated Discomforts

The IRB review of research involving children as subjects will 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 will 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.

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

(1) Research not involving greater than minimal risk.

(2) Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach.

(3) Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational settings; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

(4) Research that is 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 the above three categories may be conducted provided that the IRB (and, if funded by DHHS, 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.

Risk Determination	**Benefit Assessment**	**IRB Action**

Minimal	With or without direct benefit	Approvable
Greater than minimal risk*	Potential benefit to child	Approvable
Greater than minimal risk*	No direct benefit to individual, but offers general knowledge about the child's condition or disorder	Approvable case-by-case
Greater than minimal risk	No direct benefit to child, but offers potential to, "understand, prevent, or alleviate a serious problem affecting the health and welfare of children"	Not approvable**
* Risk may not be more than a minor increase over minimal risk, consent of both parents required under normal circumstances. **Approval to proceed with this category of research must be made by the Secretary of the HHS with input from selected experts, and following opportunity for public review and comment.		

In all cases, the IRB will determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians.

Central to the 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, the IRB 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 will 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.

In assessing the possible benefits of research intervention, the IRB will 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., meningococcus 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 will take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

Consent Process

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), in place of the consent of the subjects.

Given that children have not reached their full intellectual and emotional capacities and are legally unable to give valid consent, involving children in research requires the permission of their parents or legally authorized representatives. The IRB will determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered "not reasonably available" (examples of circumstances in which parental permission may be inappropriate are discussed below). In addition, the IRB will 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.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Category 1, minimal risk research, or Category 2, research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. Where research is covered by Categories 3 and 4, 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.

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, the IRB may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. While assent is not required to be sought from children starting at a specific age, assent will be sought when, in the judgment of the IRB, the children are capable of providing their assent, taking into account the ages, maturity, and psychological state of the children involved.

When the research offers the child the possibility of a direct benefit that is important to the health or well-being 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. 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, the IRB will 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.

When the IRB determines that the assent of the child is required, it will also determine that the provisions for obtaining and documenting assent are adequate. 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 agrees to participate.

For some research activities, the IRB 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.

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 types of cases, the IRB will consider the development of alternative procedures, on a case by case basis, for protecting the rights and interests of the children asked to participate, including, perhaps, the court appointment of special guardians.

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, the IRB may consider other alternatives, such as asking for court review of the parents' decision.

The IRB will consult legal counsel about the applicability of any state laws affecting consent for the proposed research. The IRB will make itself 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. Age 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.

Exemption From Review

The exemption (see exemption category 2 under Exemptions from IRB Review), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the Principal investigator(s) do not participate in the activities being observed. The remaining exemptions in category 2 can apply to research involving children.

Wards of the State

The federal regulations providing special protections for children 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, 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. The IRB will 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.

The IRB will 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. The IRB will 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 Principal investigator.

4. Pregnant Women, Human Fetuses, and Neonates

DHHS regulations at 45 CFR 46, subpart B provide additional protections pertaining to biomedical and behavioral research involving pregnant women, human fetuses, and neonates as subjects.

HCA Midwest Division's IRB will review research covered by this subpart and approve only research, which satisfies the conditions of all applicable sections of this subpart.

Definitions

(1) DEAD FETUS means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
(2) DELIVERY means complete separation of the fetus from the woman by expulsion or extraction or any other means.
(3) FETUS means the product of conception from implantation until delivery.
(4) NEONATE means a newborn.
(5) NONVIABLE NEONATE means a neonate after delivery that, although living, is not viable.
(6) PREGNANCY encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.
(7) VIABLE, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D.

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, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

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

(4) If the research holds out
   a. The prospect of direct benefit to the pregnant woman,
   b. The prospect of a direct benefit both to the pregnant woman and the fetus, or

c. No prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, and the woman's consent is obtained;

(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, 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 (4) and (5) is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate; and

(7) For children who are pregnant, assent and permission are obtained in accord with subpart D for studies involving children;

(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, pre-clinical 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 following requirements have been met as applicable:

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

1. The IRB determines that:
   i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
   ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

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

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

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

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

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

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

5. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A, except that the waiver and alteration provisions 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, 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.

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

Research involving, after delivery, the placenta, dead fetus or fetal material (45 CFR 46.206)

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities. For more information please contact the IRB office.

If information associated with the above mentioned material is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts are applicable.

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates (45 CFR 46.207).

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

(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 Sec. 46.204, as applicable; or
   b. The following:
      1. 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;
      2. The research will be conducted in accord with sound ethical principles; and
      3. Informed consent will be obtained in accord with the informed consent provisions of subpart A (Common Rule) and other applicable subparts.

5. Other Vulnerable Groups

Although federal regulations list vulnerable groups, other vulnerable groups may include mentally impaired persons, employees of the Sponsor or Principal investigator, terminally ill patients, and the very elderly. The IRB will determine special protections for these groups on a case-by-case basis, taking into account the risks and benefits and other protections afforded by institutional policies and state and federal law.

6. Subjects in "Treatment IND" studies

Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications, which have not been proven either safe or effective, in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risks involved. The IRB must ensure that potential subjects are fully aware of the risks involved in participation.

The IRB should also pay particular attention to Treatment Indus in which the subjects will be charged for the cost of the drugs. The question here is one of equitable selection and the involvement in research of vulnerable populations, particularly economically disadvantaged persons [21 CFR 56.111(a)(3)]. If subjects will be charged for use of the test article, economically disadvantaged persons would likely be excluded from participation. The stated purpose of the Treatment IND exemption is to facilitate the availability of promising new drugs to desperately ill patients while obtaining additional data on the drug's safety and effectiveness. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB will need to balance this interest against the possibility that unless the Sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA.

7. Cognitively Impaired Subjects

Studies involving subjects who are decisionally impaired may take place over extended periods. The IRB should consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. The IRB may require that Principal investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB should consider whether, and when, it should require a

reassessment of decision-making capacity.

8. Responsibility

IRB Administrators are responsible for maintaining up-to-date review tools for review of research pertaining to vulnerable groups based on new and evolving applicable regulations and guidelines, and for ensuring the IRB members are apprised of new and evolving regulations and guidelines pertaining to vulnerable populations. IRB members are responsible for conducting appropriate review of research planned for vulnerable populations, including an assessment of potential for coercion, in consultation with any appropriate experts and resources.

Additionally, the IRB should be familiar with the following special considerations:

1. National Commission for the Protection of Human Subjects recommendations concerning abortions (http://www.bioethics.gov/reports/past_commissions/research_fetus.pdf); and
2. The President's Council on Bioethics recommendations concerning Stem Cell Research (http://www.bioethics.gov/topics/stemcells_index.html).

9. Applicable Regulations And Guidelines

The Belmont Report
45 CFR 46: Subparts B, C, D
45 CFR 46.122
21 CFR 56.111
OHRP IRB Guidebook

B. CATEGORIES OF RESEARCH

1. Policy

The categories of research defined in these policies involve either methodologies that might require additional considerations or for which there are federally mandated determinations that all IRBs are required to make and document. These categories of research include, but are not limited to:

- AIDS Related Research
- International Research
- Medical Devices
- Investigational New Drugs
- Investigational Use of Marketed Drugs, Biologics, and Medical Devices
- Genetic Research
- Prospective Research in Emergency Settings
- Emergency Use of an Investigational Article
- Residual Body Fluids, Tissues and Recognizable Body Parts
- Protocols Lacking Plans for Human Involvement

2. AIDS Related Research

There are three ethical considerations that must be observed in the conduct of AIDS related research.

(1) THERE MUST BE FAIRNESS IN THE DISTRIBUTION OF BOTH RISKS AND BENEFITS OF RESEARCH: Caution is needed to make sure that age, competence, experience, education, position, life style, etc., are not used to determine eligibility for entrance into a study unless these factors are necessary for the research design.

(2) POSSIBLE BENEFITS OF THE RESEARCH MUST BE MAXIMIZED AND POSSIBLE HARMS MINIMIZED: As the research develops these matters will have to be reviewed from time to time to clarify what benefits may accrue to society as a whole, what benefits may accrue to subjects, and what possible harms may come to subjects. Special care must be taken to establish safeguards to prevent accidental or careless disclosure of confidential information. Improper disclosure could threaten family relationships, job security, employability or ability to obtain credit or insurance. Therefore, staff persons must be trained to handle information and data with due regard for the rights of subjects.

(3) THE RIGHTS OF RESEARCH SUBJECTS TO MAKE CHOICES BASED ON INFORMED JUDGMENTS MUST BE RESPECTED: These rights must be protected through a consent procedure which:

a. Is legally effective;
b. Is obtained in non-coercive circumstances with sufficient time and opportunity for subjects to make an informed decision;
c. Does not attempt to waive the rights of subjects, or contain exculpatory language which is intended to limit the legal liability of the institution; and
d. Is presented to subjects in language that is understandable to them--if necessary in a language other than English.

Because of the special sensitivity of AIDS research, the IRB will exercise particular care in observing all applicable regulatory provisions. The IRB will see that risks to subjects are minimized consistent with sound research design, and that risks to subjects are reasonable in relation to benefits and the importance of the knowledge that may reasonably be expected to gain. Whenever appropriate, procedures already being performed on subjects for diagnostic or treatment purposes should be used. To ensure adequate review of AIDS studies, the IRB may consult with persons who have special expertise and with persons who are qualified to represent the interests of the subject population.

3. International Research

All HCA Midwest Division research performed outside of the United States (50 states and the U.S. territories) will be subject to the following HCA Midwest Division policy, to ensure the protection of human subjects in international research studies and to comply with OHRP directives [August 27, 1998, updated July 21, 2000] requiring local context review of such studies.

Protocol review and approval is required by:

(1) The outside country's IRB, Ethical Review Committee, or equivalent organization, and
(2) HCA Midwest Division's IRB.

(3) If foreign collaborators do not have their own IRB or comparable review committee, they may designate another IRB willing to review the research as the IRB of record. That IRB could

be HCA Midwest Division's IRB or another IRB in the host country.

If foreign collaborators do have their own IRB or comparable review committee, the HCA Midwest Division Principal investigator must ensure that the host country's IRB has had current education and training in Fundamental Human Research Protections and that it has procedures in place to ensure that subjects will be protected in a manner commensurate with the Common Rule. These procedures must be described in an agreement called an "assurance of compliance" with OHRP.

The federal regulations acknowledge that local customs, norms, and laws where the research will take place may differ from the Common Rule and provide options for listing different standards in foreign assurances of compliance. Optional standards include, among others, the Canadian Tri-Council Policy, the Indian Council of Medical Research, and the CIOMS International Ethical Guidelines (biomedical).

HCA Midwest Division IRB Review

All of the HCA Midwest Division IRB policies for research studies conducted within the United States apply to international research. In addition international research protocols should include:

(1) Explanations of cultural differences that influenced the study design and the consent process;
(2) Rationale for conducting the study with an international population;
(3) Information regarding the host country's IRB, Ethical Review Committee or equivalent organization and documentation of its approval of the research, if applicable (The HCA Midwest Division IRB may require meeting minutes from the committee in the host country);
(4) A copy of the letter(s) of agreement on letterhead stationary with signatures from the local host institution(s), and from government officials (as necessary) to cooperate in the proposed research;
(5) A copy of the consent form (if used) in English, a copy in the appropriate native language(s), and a copy of the "back translation";
(6) Information regarding the literacy level of the expected subjects and how this may affect the informed consent process;
(7) Information regarding why women were or were not included in the study;
(8) A description of the informed consent process including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable subjects;
(9) A description of the processes for assuring anonymity and/or confidentiality of all data, and a description of the methods of transport and security of data to the United States, if applicable;
(10) If data will be collected by someone other than the researcher, the curriculum vitae of the individual and letters of agreement, should be included on letterhead stationary and with signatures from the research institutions;
(11) If compensation is given to subjects, justification for the amount of money or goods should be provided and an explanation as to how this compensation is proportionate to the average annual income of people in the host country.

It is the practice of the HCA Midwest Division IRB to give full board review to all research studies conducted outside the United States that include human subject contact. For studies that involve no contact with subjects and that are minimal risk (e.g., chart reviews or additional laboratory analysis of previously collected samples), expedited review of the study may be granted by the HCA Midwest Division IRB. If a minimal risk study receives expedited review, a consultant familiar with the local context will be asked to provide to the reviewer with a written

evaluation for local context review.

Special IRB Considerations:

For studies involving populations that have no written language:

- Use an English consent form as a template for translation into the oral language
- The consent form should be signed by the interpreter, the study Principal investigator, and the subject, who will be requested to make a mark or thumb print, as appropriate.
- Include a statement about the process of informed consent.

For studies involving populations that utilize group consent:

- Describe and justify the use of group consent.
- Provide a method to obtain private or individual subject assent, if possible.
- Provide a method of protecting those who choose not to participate in the study.

For "non-therapeutic" research:

- Provisions must be made for the study population to benefit from the research study.

For "therapeutic" research:

- Provisions must be made and documented to address the issue of why the study should or should not provide continued access to the experimental intervention (should it prove efficacious) or other research benefits, by the host after the completion of the study.

For Federally funded studies:

- A Federalwide Assurance is necessary to document that the international institution or performance site will conduct the research in accordance with United States Federal policies and regulations.

For studies involving minors (participants under the age of 18 years):

- The HCA Midwest Division requirements for assent for minors in research studies are applicable.

- Written, parental permission is also required. If local customs and regulations are such that active parental permission would be culturally inappropriate, the researcher must supply the IRB with proof that such permission is not culturally appropriate. Examples of such proof would be specific regulations (in English and certified to be accurate) that indicate that such permission is not required, an official letter from a ranking official in the country of interest indicating that such permission is not culturally appropriate, or the appearance at an HCA Midwest Division IRB meeting by someone of official standing in the research or academic community who can attest to the cultural inappropriateness of the requirement for active parental permission.

- In those cases where seeking active parental permission for minors to participate in research is culturally inappropriate, a waiver of such permission may be granted at the discretion of the HCA Midwest Division IRB, as long as the research does not place the participant(s) at untoward risk. Regardless of the type of risk, the participant(s) in the research retain(s) the right to discontinue participation, without penalty, at any time.

- If a waiver of active parental permission is granted, and if a letter informing the parents of the research is deemed appropriate, it must be written at a literacy level that would be understood by the parents, and should be sent to them by the most expeditious method

possible. HCA Midwest Division's IRB will review the "back translation" of this letter.

Local Context Consultant:

The key requirement for local context review is that a person who is familiar with the customs and culture of the study population participates in the review at the HCA Midwest Division IRB meeting. Consultants must be native to the country, have had knowledge of such customs and culture that was obtained through extended, direct experience in the community, or be a professional familiar with the local environment. The consultant will attend, in person or via telephone, convened HCA Midwest Division IRB meetings as an *ad hoc* non-voting member of the HCA Midwest Division IRB. Information on the protocol will be sent to the local context consultant at least one week in advance of the convened meeting. The review and recommendations of the consultant will be documented in the HCA Midwest Division IRB minutes.

The Chairperson of the HCA Midwest Division IRB or, if designated by the Chairperson, the IRB Administrator, will interview potential consultants and inform them of the responsibilities of local context consultants.

Continuing Review:

A protocol will have only one local context review unless there are significant changes in the protocol or the risks to the subjects. HCA Midwest Division's standard continuing review requirements will apply to international research studies.

4. Medical Devices

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

Humanitarian Device Exemption: A humanitarian device exemption (HDE) is submitted for FDA review and approval by a manufacturing company/company/sponsor. The purpose of the HDE is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States. Although a device may have HDE approval, it still falls under the category of an HUD.

Humanitarian Device Exemption Final Rule Summary: An HUD is approved for marketing through an HDE application filed in accordance with the requirements of this final rule. An HDE application is a PMA application that is not required to contain clinical data demonstrating "effectiveness" (defined under Sec. 860.7(e)(1) (21 CFR 860.(e)(1)) as "reasonable assurance…based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results"). An HDE application will contain all other information ordinarily required in a PMA. In addition, an HDE application will require certain special information to satisfy the statutory requirements established by section 520(m) of the act, http://www.fda.gov/orphan/humuse.htm.

Humanitarian Device Exemption Holder: the company providing the device. The company providing the device is responsible for ensuring that the HUD is only used in facilities having an IRB or Central IRB agreement constituted and acting in accordance with 45 CFR Part 56; is required to maintain records of the names, addresses of the facilities to which the HUD has been shipped, is required to maintain copies of correspondence with reviewing IRBs as well as any other information required by the reviewing IRB or FDA.

Humanitarian Use Device: An HUD is a device that is (1) intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year; (2) the device would not be available to a person with such a disease or condition unless the exemption is granted; (3) no comparable device (other than a device that has been granted such an exemption) is available to treat or diagnose the disease or condition; and (4) the device will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

Humanitarian Use Device IRB Approval: Section 520(m)(4) of the act states that an HUD may only be used in facilities that have established, in accordance with FDA regulations, "a local institutional review committee [commonly known as an institutional review board or IRB] to supervise clinical testing of devices in the facilities." The statute also requires an IRB to approve the use of the HUD before the device is administered to humans. In accordance with this statutory requirement, FDA has specified in subpart H of part 814 that the HDE holder must ensure that the HUD is administered only to patients at health care facilities having an IRB. IRBs which oversee the use of an HUD should be constituted and act in accordance with the agency's regulations governing IRBs (21 CFR part 56), including responsibility for continuing review of use of the device. FDA has codified this requirement in Sec. 814.124. The agency does not believe the statute intends to require IRB review and approval for each individual use of the HUD. FDA has interpreted the statute to permit the IRB to approve the use of the device in general, use of the device for groups of patients meeting certain criteria, or use of the device under a treatment protocol. If it so wishes, an IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB chair, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate. It should be emphasized that under the final rule (Sec. 814.124), it is the HDE holder who is responsible for ensuring that the HUD is not administered to or implanted in a patient prior to obtaining IRB approval at the health care facility. An HDE holder may wish to enforce this requirement by not shipping the HUD to the health care facility until it has received confirmation of IRB approval. In order to provide flexibility to the approval requirement, FDA has included a provision that permits an IRB located at a treatment facility to defer (in writing) to another similarly constituted IRB that has agreed to assume responsibility for initial and continuing review of the use of the device, http://www.fda.gov/orphan/humuse.htm.

All Company-affiliated facilities must ensure that IRB review and IRB approval of an HUD/HDE occurs before the HUD/HDE is administered to or implanted in a patient. Although there are provisions for emergency use of an investigational device without IRB approval (see the Informed Consent IRB Review Policy, QM.RES.003, these provisions are not intended as a “loophole” to circumvent the IRB approval procedures whenever prior review is possible.

1. IRBs are responsible for a full Board review of the initial submission of the request to use an HUD/HDE. Expedited review is not allowed for the initial review.

2. For continuing review of an HUD/HDE, IRBs may use the expedited review procedure unless the IRB determines at the time of initial review that full board review should be performed. Expedited review procedures are appropriate for continuing review since the initial review would have been performed by the full board and use of an HUD/HDE within its approved labeling does not constitute research.

Investigational Device Exemption (IDE)

An investigational device is a medical device, which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR 812].

The following clinical investigations of devices may be exempt from the IDE regulations [21 CFR 812.2(c)].

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined 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 part 807 in determining substantial equivalence.
(3) A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.10(c) and if the testing:
    a. Is noninvasive,
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
(4) A device undergoing 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.
(5) A device intended solely for veterinary use.
(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).
(7) A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "non-significant risk" (NSR). The determination that a device presents a non-significant or significant risk is initially made by the sponsor. The proposed study is then submitted to FDA, for SR studies, or to the IRB, for NSR studies.

The sponsor/Principal investigator should provide the IRB with the following information:

(1) A risk assessment,
(2) The rationale used in making the risk determination,
(3) A description of the device,

(4) Reports of prior investigations with the device,
(5) The proposed investigational plan,
(6) A description of patient selection criteria and monitoring procedures,
(7) Information regarding whether other IRBs have reviewed the proposed study and what determination was made, and
(8) FDA's assessment of the device's risk if such an assessment has been made.

The IRB will review the above-mentioned material, and make a final risk determination based on its own review. The IRB may also consult with FDA for its opinion.

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

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

If a Principal investigator or a sponsor proposes the initiation of a claimed NSR investigation to the IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin immediately, without submission of an IDE application to FDA. If the IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with the IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to the IRB as an NSR investigation.

SR versus NSR

An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; (2) is used in supporting or sustaining human life; (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; OR (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk."

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

(1) The study of a pacemaker that is a modification of a commercially-available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker will only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.
(2) The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

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

Examples of NONSIGNIFICANT RISK DEVICES: (1) Low Power Lasers for treatment of pain, (2) Caries Removal Solution, (3) Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions), (4) Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use, (5) Conventional Gastroenterology and Urology Endoscopes and/or Accessories, (6) Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular), (7) Conventional Implantable Vascular Access Devices (Ports), (8) Conventional Laparoscopes, Culdoscope, and Hysteroscope, (9) Dental Filling Materials, Cushions or Pads made from traditional materials and designs, (10) Denture Repair Kits and Recliners, (11) Digital Mammography [Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.], (12) Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities), (13) Externally Worn Monitors for Insulin Reactions, (14) Functional Electrical Neuromuscular Stimulators, (15) General Biliary Catheters General Urological Catheters (e.g., Foley and diagnostic catheters), (16) Jaundice Monitors for Infants, (17) Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters, (18) Manual Image Guided Surgery, (19) Menstrual Pads (Cotton or Rayon, only), (20) Menstrual Tampons (Cotton or Rayon, only), (21) Nonimplantable Electrical Incontinence Devices, (22) Nonimplantable Male Reproductive Aids with no components that enter the vagina, (23) Ob/Gyn Diagnostic Ultrasound within FDA approved parameters, (24)

Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain, (25) Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings).

Examples of SIGNIFICANT RISK DEVICES:

(1) *General Medical Use*
Catheters:
*Urology - urologic with anti-infective coatings
*General Hospital - except for conventional long-term percutaneous, implanted, subcutaneous, intravascular
*Neurological - cerebrovascular, occlusion balloon
*Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system
Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications
Surgical Lasers for use in various medical specialties
Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology.

(2) *Anesthesiology***:** Breathing Gas Mixers, Bronchial Tubes, Electroanesthesia Apparatus, Epidural and Spinal Catheters, Epidural and Spinal Needles, Esophageal Obturator, Gas Machines for anesthesia or analgesia, High Frequency Jet Ventilators greater than 150 BPM, Rebreathing Devices, Respiratory Ventilators, Tracheal Tubes.

(3) *Cardiovascular:* Aortic and Mitral Valvoplasty Catheters, Arterial Embolization Devices Cardiac Assist Devices [artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices], Cardiac Bypass Devices [oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices], Cardiac Pacemaker/Pulse Generators [antitachycardia, esophageal, external transcutaneous, implantable], Cardiopulmonary Resuscitation (CPR) Devices, Cardiovascular/Intravascular Filters, Coronary Artery Retroperfusion Systems, Coronary Occluders for ductus arteriosus/atrial/septal defects, Coronary and Peripheral Arthrectomy Devices, Extracorporeal Membrane Oxygenators (ECMO), Implantable Cardioverters/Defibrillators, Laser Coronary and Peripheral Angioplasty Devices, Myoplasty Laser Catheters, Organ Storage/Transport Units, Pacing Leads, Percutaneous Conduction Tissue Ablation Electrodes, Peripheral/Coronary/Pulmonary/Renal/Vena Caval/Peripheral Stents, Replacement Heart Valves, RF Catheter, Ablation and Mapping Systems, Ultrasonic Angioplasty Catheters, Vascular and Arterial Graft Prostheses, Vascular Hemostasis Devices.

(4) *Dental*: Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications, Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA), Dental Lasers for hard tissue applications, Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants, Subperiosteal Implants, Temporomandibular Joint (TMJ) Prostheses.

(5) *Ear, Nose, and Throat*: Auditory Brainstem Implants, Cochlear Implants, Laryngeal Implants, Total Ossicular Prosthesis Replacements.

(6) *Gastroenterology and Urology:* Anastomosis Devices, Balloon Dilation Catheters for benign prostatic hyperplasia (BPH), Biliary Stents, Components of Water Treatment Systems for Hemodialysis, Dialysis Delivery Systems, Electrical Stimulation Devices for sperm collection, Embolization Devices for general urological use, Extracorporeal Circulation

Systems, Extracorporeal Hyperthermia Systems, Extracorporeal Photopheresis Systems, Femoral/Jugular/Subclavian Catheters, Hemodialyzer, Hemofilter, Implantable Electrical Urinary Incontinence Systems, Implantable Penile Prostheses, Injectable Bulking Agents for incontinence, Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic), Mechanical/Hydraulic Urinary Incontinence Devices, Penetrating External Penile Rigidity Devices with components that enter the vagina, Peritoneal Dialysis Devices, Peritoneal Shunt, Plasmapheresis Systems, Prostatic Hyperthermia Devices, Urethral Occlusion Devices, Urethral Sphincter Prostheses, Urological Stents (e.g., ureteral, prostatG).

(7) *General and Plastic Surgery:* Absorbable Adhesion Barrier Devices, Absorbable Hemostatic Agents, Artificial Skin and Interactive Wound and Burn Dressings, Injectable Collagen, Implantable Craniofacial Prostheses, Repeat Access Devices for surgical procedures, Sutures.

(8) *General Hospital*: Implantable Vascular Access Devices (Ports) - if new routes of administration or new design, Infusion Pumps (implantable and closed-loop - depending on the infused drug).

(9) *Neurological***:** Electroconvulsive Therapy (ECT) Devices, Hydrocephalus Shunts, Implanted Intracerebral/Subcortical Stimulators, Implanted Intracranial Pressure Monitors, Implanted Spinal Cord and Nerve Stimulators and Electrodes.

(10) *Obstetrics and Gynecology*: Antepartum Home Monitors for Non-Stress Tests, Antepartum Home Uterine Activity Monitors, Catheters for Chorionic Villus Sampling (CVS), Catheters Introduced into the Fallopian Tubes, Cervical Dilation Devices, Contraceptive Devices [Cervical Caps, Condoms (for men) made from new materials (e.g., polyurethane), Contraceptive *In Vitro* Diagnostics (IVDs), Diaphragms, Female Condoms, Intrauterine Devices (IUDs), New Electrosurgical Instruments for Tubal Coagulation, New Devices for Occlusion of the Vas Deferens, Sponges, Tubal Occlusion Devices (Bands or Clips)], Devices to Prevent Post-op Pelvic Adhesions, Embryoscopes and Devices intended for fetal surgery, Falloposcopes and Falloposcopic Delivery Systems, Intrapartum Fetal Monitors using new physiological markers, New Devices to Facilitate Assisted Vaginal Delivery, Thermal Systems for Endometrial Ablation.

(11) *Ophthalmics:* Class III Ophthalmic Lasers, Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use, Corneal Implants, Corneal Storage Media, Epikeratophakia Lenticules, Extended Wear Contact Lens, Eye Valve Implants (glaucoma implant), Intraocular Lenses (IOLs) [21 CFR part 813], Keratoprostheses Retinal Reattachment Systems [fluids, gases, perfluorocarbons, perfluorpropane, silicone oil, sulfur hexafluoride, tacks], Viscosurgical Fluids.

(12) *Orthopedics and Restorative***:** Bone Growth Stimulators, Calcium Tri-Phosphate Hydroxyapatite, Ceramics Collagen and Bone Morphogenic Protein Meniscus Replacements, Implantable Prostheses (ligament, tendon, hip, knee, finger), Computer Guided Robotic Surgery.

(13) *Radiology*: Boron Neutron Capture Therapy, Hyperthermia Systems and Applicators.

IRB and Sponsor Responsibilities Following SR/NSR Determination

If the IRB decides the study is Significant Risk:

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

(2) Sponsor Responsibilities:
   a. Submit IDE to FDA or, if electing not to proceed with study, notify FDA of the SR determination;
   b. Study may not begin until FDA approves IDE and IRB approves the study.
   c. Sponsor and Principal investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

If the IRB decides the study is Nonsignificant Risk:

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

IRB Review of the Protocol and Informed Consent

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

5. Investigational New Drugs (IND)

An IND application must be filed when:

(1) A sponsor wishes to test a newly developed drug to see if its safety and efficacy are such that it can be approved for marketing,

(2) For studies of drugs that are already licensed if the intent of the study is to generate data that will lead to approval of a new advertising claim, a new clinical indication, or a new formulation of the product, and

(3) To add a new study design, a new patient group, or a new clinical indication to the evaluation of a product that is under study but not yet marketed.

If a drug is already licensed and approved by the FDA for marketing in the United States, it may be studied without an IND, as long as the study is not designed to change the approved indications, advertising claims, or labeling of the product. The study must not be one that

changes dose, route of administration, or target population in a way that is likely to increase risk. The study is still subject to all of the usual requirements for IRB oversight, and the study must not violate any of the FDA's rules about advertising and promotion of drugs.

Once FDA approval has been secured, Principal investigators should submit the study along with the necessary submission materials to the IRB. The IRB will ensure that the data will be kept secure, and will be monitored for safety issues as well as for study quality.

Adverse events must be reported, both to the FDA and to the IRB. Changes in protocols must be submitted for approval, both to the FDA and to the IRB, and may not be implemented until approved by both, unless their purpose is to protect subjects from serious harm (for example, by removing a newly recognized substantive risk).

A sponsor may withdraw an IND at any time, with or without cause. The FDA may also terminate an IND under a number of circumstances. A "clinical hold" is a suspension of an IND, during which no new subjects may be enrolled, and subjects who have already been enrolled may only continue the study drug if it is clinically necessary for them to do so. This action may be taken when it appears that subjects are being exposed to greater risk than had originally been recognized; the IND and the study are then often reactivated when appropriate adjustments in study design have been made. A "clinical hold" may also result if the researchers' qualifications are called into serious question, or if the study design proves flawed in a way that precludes meaningful results.

More serious deficiencies may lead to termination of an IND. In that case, reactivation is not foreseen and the project is shut down. If the cause is clear and compelling danger to research subjects, this may be a rather precipitous action. If it is for problems in study conduct that do not place subjects at increased risk, the FDA will ordinarily notify the sponsor of the intent to terminate the IND and give the sponsor an opportunity to respond.

6. Investigational Use of Marketed Drugs, Biologics, and Medical Devices

"Investigational use" suggests the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE is required.

However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(1) It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
(2) It is not intended to support a significant change in the advertising for the product;
(3) It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
(4) It is conducted in compliance with the requirements for IRB review and informed consent;
(5) It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
(6) It does not intend to invoke 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research.

HCA Midwest Division's IRB will review studies submitted with IND exemption requests to determine whether they meet the above exemption criteria. If the IRB determines that the

exemption criteria are not met or the IRB is not certain whether the exemption criteria are met and an IND has not been obtained, it will ask the Principal investigator to submit an IND or have the FDA make a determination on the requirement for an IND. If the FDA determines that an IND is not necessary, it will provide an exemption letter. A copy of this letter should be provided to the IRB. Should the FDA determine that an IND is required; a complete IND application must be submitted to the FDA for review. Upon completion of review, the FDA will send the Principal investigator a letter. The IRB will withhold approval of the study until the Principal investigator provides a copy of either the FDA determination letter or the IND number provided by the FDA.

IND application and approval/exemption is specific to the protocol rather than to the drug. Any proposed modifications to the protocol that significantly affect the safety of the subject or the scope of the investigation (e.g., a new protocol with the same drug) must be submitted to the FDA for review.

7. Genetic Research

Genetic research may require special considerations.

a. Type of Review: At first consideration, much genetic research may *appear* to meet the criteria for expedited review. These include:
   1. Pedigree studies, which look for a pattern of inheritance of a gene;
   2. Positional cloning studies, which are conducted to identify particular genes;
   3. Diagnostic studies, which gather samples to develop techniques to determine the presence of specific DNA mutations.

   However, these studies may create a vulnerable population in that subjects' autonomy may be compromised. Therefore the full IRB must review these studies to answer the following questions:
   (1) Will the samples be made anonymous to maintain confidentiality? If not, to what extent will the results remain confidential; and who will have access to them?
   (2) Will the samples be used for any additional studies not made explicit at the time of donation, or will the samples be destroyed after specified, one-time use?
   (3) Will the donor be informed of any and all results obtained from his or her DNA? Will the donor be informed of the results of the entire study?
   (4) Will family members be implicated in the studies without consent?

b. Privacy and Confidentiality Issues: Privacy and confidentiality issues are one of the most challenging regulatory aspects of genetic research. Because of the sensitive nature of the information that may be generated from genetic research studies, it is critical that Principal investigators establish a method to secure information in a highly confidential manner. Studies that have the potential to ultimately predict the likelihood of subsequent serious illness could place participants at high risk for psychological and social harm. This type of sensitive information could adversely affect an individual's future insurability and employability as well as have significant impact on his or her psychological well being. Thus, IRB review must be scrupulous in assuring that privacy and confidentiality are always maintained.

   As genetic research may yield information of the most private nature, the IRB and potential research subject must understand exactly who will have access to study information and under what circumstances. This issue of disclosing research results to the subject should be explicitly addressed in the protocol and consent. Principal investigators and IRBs have to

weigh the risks and benefits of giving a subject access to research results. Something that may be overlooked is the possibility that the disclosure of unanticipated or incidental information may harm the subject. An additional important consideration is the potential need for genetic counseling. It is impossible to clearly define the situations for which counseling is indicated, but IRBs should consider the potential benefits of genetic counseling to participants in these studies.

c. Use of Tissue or Cell Banks: Genetic studies often involve the use of tissue or cell banks that may involve the long-term storage of biological materials. Because the results of future studies may pose harm to individuals, it is crucial that participants be fully informed about their subsequent knowledge or research results. Whenever possible, genetic test results should be stored in a secure manner. During the informed consent process, it is critical that participants understand both the inherent risk of this type of research and, if it is the case, that they will not be informed of the results of subsequent studies performed on their tissue.

d. Subjects' Rights to Withdrawal: Ethical research requires that subjects have the right to withdraw from research participation at any point in the study. In genetic research, there is the potential for continuation of individual risk after withdrawal from the study when there is long-term storage of tissue. For this reason, it is important to determine if the research plan provides for the destruction of all stored data and tissue if the subject wants this to be done. If the research plan does not provide for tissue or data destruction, the study may still be ethical as long as participants understand this limitation.

e. IRB Review: A critical first step in the IRB review process of genetic studies is the determination of the predictive value of the study results. If there is reasonable scientific evidence that the expression of certain genetic markers within a study accurately predicts for a particular disease or condition, then participants are at risk, and the IRB must know the answers to a detailed list of questions before a determination can be made:
    1. Are clear guidelines established for disclosure to participants of interim or inconclusive research results?
    2. Will participants be informed of research results at each point in the research?
    3. If information is discovered about the participant that may have implications for biologic family members, what are the plans to protect confidentiality?
    4. Will limits on such protections be clearly communicated to participants, including obtaining advance consent to such disclosures (e.g., when family members will be warned about health risks)?
    5. Will the possible psychological and social risks of genetic research be adequately considered in the consent process?
    6. Will appropriate counseling be provided, both as part of the consent process and when communicating test or other research results to participants?
    7. Will participants be informed about the possibility of important incidental findings such as paternity, disease, or conditions other than the one(s) that is/are the focus of the study?
    8. Will the data be protected from disclosure to third parties, such as employers and insurance companies?
    9. Will the participant be told about the potential consequences if a third party becomes aware of the study findings?
    10. Will the data be stored in a secure manner?
    11. Will the data be coded so as to protect the identity of the subjects?
    12. Is a request for a certificate of confidentiality appropriate?

13. Does the PI plan to disclose research findings to subjects' physicians for clinical use? Are such plans appropriate?
14. Will the possibility of such disclosures be discussed in the consent process?
15. Will vulnerable populations be adequately protected?
16. Under what circumstances can a research participant give permission to involve a minor or an adult who lacks decision-making capacity in an aspect of this study?
17. What are the provisions for protecting the confidentiality of tissue samples?
18. What procedures will be used to get the subject's permission to store tissue or data for additional research in the future or for non-research medical practice?
19. What will happen to research data and tissue if a subject elects to withdraw from the study?
20. Are the implications of study withdrawal in terms of destruction or use of established data or tissue clearly explained in the consent document?
21. Do the plans to publish or present data from this study threaten the privacy or confidentiality of participants?
22. If the research may involve family members:
    a. Is the strategy for recruiting family members sensitive to privacy and confidentiality issues?
    b. Will information be obtained from the medical records of family members?
    c. If so, should consent be obtained from the family members to access this information?

Alternatively, if there is no clear evidence that a particular marker has predictive value, then there is virtually no risk to participants.

f. Informed Consent: The following information should be included in the consent document:
1. Clearly explain whether the subjects will have access to information obtained as part of this study. Explain what information they will be given whether they ask for it or not.
2. Explain if subjects may learn things about themselves or their family that they do not want to know, or that they may be uncomfortable knowing.
3. Explain if family members may learn about information generated in this study and the potential implications of this knowledge.
4. Explain if participation in this study may compromise the subjects' insurability.
5. Explain if participation in the study may prompt the subject to take actions that may incur unanticipated costs or expose the subject to additional risks (i.e. genetic counseling may be expensive).
6. Accurately describe the limitations of protection of privacy and confidentiality.
7. Explain what it means to withdraw from this study in terms of the destruction or use of data or tissue related to the study.
8. Include an appropriately detailed explanation of all costs that are likely to be incurred by the subject or family members as a result of participation in the study. Address both the costs of procedures required by the study and costs, like genetic counseling, additional genetic testing, or psychological counseling, that the subject or family may be advised to pay based on study results.

g. Gene Therapy Research:
Gene therapy research (administration of recombinant vectors), which is carried out to develop treatments for genetic diseases at the DNA level, presents obvious and not so obvious questions, including – considerations of delivery methods, target population, and required follow-up. Such protocols will likely require use of external consultants to provide independent guidance to the IRB. If the project involves gene therapy to human subjects for other than clinical purposes, the study must be reviewed and approved by the National

Institutes of Health Recombinant DNA Advisory Committee prior to IRB approval. Monitoring must be adequate, and a DSMB will be required. Because there is still little regulatory guidance and relatively few ethical precedents, genetic research will require close scrutiny, and the input of experts in this area.

8. Research in Emergency Settings (Review Obtained Prospectively)

a. The IRB, with the concurrence of a licensed physician who is either a member of IRB or a consultant, and who is not participating in the research being reviewed, may waive the requirement for informed consent in certain emergency research ONLY if it finds and documents the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:
a. The subjects will not be able to give their informed consent as a result of their medical condition;
bathe intervention under investigation must be administered before consent from the subject's legally authorized representatives is feasible; and
c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:
a. Subjects are facing a life-threatening situation that necessitates intervention;
b. Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
c. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational or research plan:
a. Defines the length of the potential therapeutic window based on scientific evidence, and
b. The Principal investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and,
c. If feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.

(6) The Principal investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

b. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.

c. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with applicable regulations.

d. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
   (1) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

   (2) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

   (3) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

   (4) Establishment of an independent DSMB to exercise oversight of the clinical investigation; and

   (5) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the Principal investigator has committed, if feasible, to attempting to contact, within the therapeutic window, the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The Principal investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

e. The study plan must ensure that, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member is informed of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.

f. The study plan must ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

g. If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided above or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the Principal investigator and to the Sponsor of the clinical investigation.

9. Emergency Use of Investigational Articles (Review Obtained Retrospectively)

a. An investigational article may be used in an emergency prior to IRB review, provided that the patient is in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

b. Such emergency use must be reported to the IRB within 5 working days, and any subsequent use of the test article is subject to prior review.

c. In such a situation, obtaining informed consent shall be considered feasible except in certain emergency situations where the Principal investigator has adequately documented the necessary exception under the guidelines described in 21 CFR 50.23. The Principal investigator must submit documentation to the IRB for review within 5 working days after emergency use of the test article. In review of the documentation, the IRB will ensure that the Principal investigator and a physician not otherwise participating in the clinical investigation have adequately certified the following in writing prior to use of the test article:

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

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

   3. Time was not sufficient to obtain consent from the subject's legal representative.

   4. There was no alternative method of approved or generally recognized therapy available that provided an equal or greater likelihood of saving the life of the subject.

d. If immediate use of the test article is, in the Principal investigator's opinion, required to preserve the life of the subject, and time is not sufficient, prior to administering the test article, to obtain an independent physician's opinion, the determinations of the Principal investigator must be reviewed in writing within 5 days after the use of the test article by a physician not otherwise participating in the clinical investigation. In this event, a copy of the independent review must be submitted to the IRB within 7 working days after the use of the test article.

e. Whenever emergency care is initiated without prior review and approval, the patient may *not* be considered to be a research subject. HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval.

f. For DHHS-supported or conducted research, the physician may, without prior IRB approval, treat the patient/subject using a test article (if the situation meets the FDA requirements), but the subject may not be considered a research subject and data derived from use of the test article may not be used in the study.

10. Residual Body Fluids, Tissues and Recognizable Body Parts

Body Fluids & Tissues: Research on existing specimens ("on the shelf" or frozen) without identifying information (e.g., no names, initials, hospital number, etc.) should be submitted to the IRB for review. Such research may be considered under expedited review, or may be exempted, but the application should be submitted for review and must include a short description of the research and where the tissue is coming from.

11. Protocols Lacking Definite Plans for Human Involvement

a. Certain types of activities are planned and written with the knowledge that human subjects may be involved, but without definite plans for such involvement. Examples of such proposed activities are:

   1. Training programs in which individual training projects remain to be selected or designed.

   2. Research, pilot or developmental studies in which the involvement of human subjects depends on such things as the completion of survey instruments or prior animal studies.

b. The IRB can give "General Approval" to programs like those mentioned above with the understanding that the specific research protocol will be submitted to them once it has been developed. "General Approval" is not appropriate for individual projects or to meet grant deadlines.

12. Responsibility

IRB Administrators are responsible for maintaining up-to-date review tools for review of research pertaining to these categories based on new and evolving applicable regulations and guidelines. IRB Chairperson and Administrators are responsible for ensuring members are well versed in new and evolving regulations and guidelines pertaining to these categories, for identifying reviewers with appropriate expertise to conduct the reviews of such research, and for securing appropriate consulting expertise as needed for selected reviews. IRB Members are responsible for conducting appropriate review of research planned for these categories in consultation with any appropriate experts and resources.

13. Applicable Regulations and Guidelines

21 CFR 812
21 CFR 312
21 CFR 50.24
21 CFR 56.104
45 CFR 46.101, 46.103, 46.118, 46.119

X. REVIEW THROUGHOUT THE STUDY'S APPROVAL PERIOD

A. POLICY

Principal investigators have a continuing responsibility to inform the IRB of:
(1) All modifications or addenda to the protocol or consent form,
(2) Adverse Events, Serious Adverse Events, and Unanticipated Problems.
(3) Any circumstances or new information, which might change the perception of a favorable risk/benefit ratio, and
(4) Protocol Deviations.

The IRB will review the aforementioned reports as they are received throughout a study's approval period. IRB approval for the conduct of a study may be withdrawn if the risks to the subjects are determined to be unreasonably high, for example, more than an expected number of adverse events, unexpected serious adverse events; or evidence that the Principal investigator is not conducting the investigation in compliance with IRB or Institutional guidelines. Such findings may result in more frequent review of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken, or the study terminated.

B. AMENDMENTS/ADDENDA TO APPROVED PROTOCOLS

It is the responsibility of the Principal investigator to submit all amendments and addenda to approved protocols for review and approval by the IRB before implementation. Changes may not be initiated without prior IRB review (full or expedited review as appropriate) and approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Amendments/addenda require review through one of the following mechanisms:
(1) Expedited Review of Amendments/Addenda: Amendments, which represent minimal risk changes to a project, may receive expedited review by the IRB Chairperson (for a list of minimal risk changes, refer to the section on 'Expedited Reviews'). If the Chairperson determines that the change represents a minimal risk revision, approval may be granted. If, however, the Chairperson determines that the amendment/addendum does not qualify for an expedited review, the amendment request will be presented to the full Board for review and comments.

(2) Full IRB Review of Amendments/Addenda: Amendments and/or addenda that do not qualify for expedited review will be decided at a convened meeting of the full IRB. Such changes include, but are not limited to the following:
   a. Proposals to add an investigational new drug or device to an already approved study,
   b. Changes that are perceived to significantly affect the risk/benefit ratio for subjects,
   c. Changes made as a result of significant or unexpected toxicity in subjects,
   d. Principal investigator changes,
   e. Significant revision of eligibility criteria, to include or exclude study participants,
   f. Introduction of a new procedure or instrument,
   g. Revision of the consent process,
   h. Addition of a new subject population,
   i. Changes in the duration of subject participation period, and
   j. Addition of procedures to audiotape and/or videotape subjects.

During a review of amendments/addenda, the IRB will address the following:
(1) Is this a minor amendment/addendum to the protocol or informed consent document?

(2) Does the Principal investigator's rationale for the amendment/addendum make sense?
(3) Is this proposal the result of an adverse event?
(4) Does this amendment/addendum alter, in any way, the assessment of potential risks as described in the originally approved protocol?
(5) If "yes," is this additional risk justified?
(6) Are there potential benefits of this proposal?
(7) If "yes," do these potential benefits outweigh the potential risks?
(8) Does the amendment/addendum require the Principal investigator to submit a revised protocol?
(9) Does the amendment/addendum require the Principal investigator to submit a revised consent form?
(10) Does the amendment/addendum change the overall risk level for this study?
(11) How often should this study be reviewed by the IRB?

If the IRB approves the amendment/addendum, it will not change the approval/renewal date of a project. If the amendment/addendum changes the risk/benefit ratio, the IRB may require the study to be reviewed more frequently.

If the IRB does not approve the amendment/addenda, it will either recommend changes for the Principal investigator to consider, or recommend that the Principal investigator utilize the previously approved protocol, as is; either way, this will not change the approval/renewal date of the project. Detailed information regarding the review and further requirements will be provided to the Principal investigator in a formal letter, within ten days of the meeting date of the review.

Emergency Protocol Changes

Rarely, a Principal investigator may have to make an immediate change in the protocol to protect the safety of research participants. In these instances, the Principal investigator should take *immediate action* to safeguard the health of the participants. If it is not possible for the Principal investigator to notify the IRB prior to an emergency action, the Principal investigator must notify the IRB in writing within 24 hours of the change in protocol, the circumstances that required its immediate implementation and a revised consent form, if necessary.

Methods to Ensure Principal investigators Do Not Implement Protocol Changes Without Prior IRB Approval

In order to ensure that Principal investigators do not implement protocol changes without prior IRB approval, the IRB office will conduct random audits of research records, and training programs for Principal investigators. In addition, specific directives will be included in approval letters to Principal investigators.

C. SERIOUS ADVERSE EVENTS (SAES)

Definition: Adverse Event (AE): Any untoward occurrence in a patient or clinical investigation subject which does not necessarily have to have a causal relationship with their participation in the study. Adverse Drug Experiences and Adverse Drug Reactions may be Adverse Events (AEs) as do abnormal lab findings, symptoms or disease concurring with the research. Adverse events may also be non-medical in nature such as economic or social harms.

Serious Adverse Event (SAE): An adverse event that results in any one of the following: 1) Death; 2) Life Threatening condition; 3) Hospitalization (or prolongation of an existing hospitalization); 4) Congenital anomaly; 5) Persistent or significant disability/incapacity; or 6) the need for intervention to prevent any one of the above criteria.

Unexpected Adverse Event (UAE): Any adverse event for which the specificity or severity is not consistent with the current investigator brochure, OR, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unanticipated" refers to an adverse event that has not been previously observed. An unanticipated problem must be reported to the IRB if the following conditions exist:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome.)

2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy.)

3. Multiple occurrences of an AE that, based on an aggregate analysis is determined to be an unanticipated problem. There should be a determination that the series of AEs represent a signal that the AEs were not just isolated occurrences and involve risk to human subjects (i.e., a comparison of rates across treatment group's reveals higher rate in the drug treatment arm versus a control).

4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. (21 CFR 312.32 (a)

If adverse consequences or unexpected side effects are encountered in the course of the study, or new information becomes available which could change the perception of a favorable risk/benefit ratio, or changes the inclusion/exclusion criteria, the Principal investigator is responsible for informing the IRB PROMPTLY. Based on this information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

With multi-center studies, the PI may satisfy his/her obligation to notify the IRB of unanticipated problem by providing the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB, and because the investigator was copied on the report from the sponsor to the IRB, FDA intends to exercise its enforcement discretion and would not expect an investigator to provide the IRB with a duplicate copy of the report received from the sponsor.

The investigational device exemption (IDE) regulations define an 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 CFR 8123 (s)).

For device studies investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.1509a)(1)).

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§812.46(b), 812.150(b)(1).

Principal investigators must report SAEs to the IRB within 48 hours of discovery, and 24 hours for deaths. For studies that have been determined by the IRB to be greater than minimal risk, these reports should be filed regardless of whether the SAE appears to be study related or is anticipated. For minimal risk studies, Principal investigators must report only SAEs that they believe are probably or definitely study-related. It is the IRB's responsibility (not the Principal investigator's) to determine which studies are classified as minimal risk. Follow up reports and a final written report should be sent to the IRB as soon as the Principal investigator receives additional information regarding the event.

The IRB Administrator will forward copies of the serious adverse events to the IRB Chairperson/designee for immediate review. The IRB Chairperson/designee will review the SAEs and may ask for additional information from the Principal investigators, such as hospital records, death certificates, pathology or autopsy reports, or request that it be reviewed by another reviewer, if necessary. The IRB Chairperson/designee will determine, to the best of his/her abilities, whether the SAE's relationship to the study is unknown, probably related, possibly related, and unlikely related, or not related. S/he will also make recommendations to the IRB regarding if protocol or consent form changes are necessary; and if so, what they are.

The IRB Administrator will contact the Principal investigator if the Chairperson/designee requires more information, or if s/he is requesting any protocol or consent form changes.

AEs, SAEs and safety reports will be logged in IRBManager data base where they will be available for review by all IRB members. The IRB will only be required to review AEs, SAEs and safety reports occurring at HCA study sites at convened meetings of the full board.

Reviewing SAEs:

At each convened meeting, the IRB reviews all new SAE's that have been reported since the last convened meeting. If protocol or consent form changes have been recommended by either the Principal investigator or the IRB Chairperson/designee, the IRB will make the decision to accept/reject these proposed changes or to require new ones. The IRB may require more frequent review to monitor the protocol. In rare instances it may become obvious to the Chairperson and the Board that a study carries an unacceptable, unanticipated risk, and the Principal investigator may be asked voluntarily to suspend the study, if he or she has not already done so, pending its re-evaluation. If the problem is deemed of sufficient magnitude, the IRB will direct the IRB Office to promptly report the injury or unanticipated problem involving risks to subjects to the appropriate institutional officials, OHRP, and any other sponsoring Federal department or agency.

1. Promptness of review should depend on the severity of the event. The institution may choose to stratify severity of events and how quickly they should be reviewed and analyzed by the IRB. This should be defined in the local SOP.

2. Questions that may be considered when reviewing an event include:
    a. Date and Time of onset of adverse event.
    b. Was the event/problem from this institution, or another participating site if a multi-center sponsor or study?
    c. Was the event/problem deemed mild, moderate, severe, or fatal? Will need date of death, including copy of the death certificate and autopsy report.
    d. Was the event/problem expected or unexpected?
    e. Was the event/problem related to the research intervention?
    It helps to specify with descriptives such as:
    Causative: probable, inconclusive, and unlikely;
    Study Related: definitely, probably, possibly, probably not related to the study.
    f. What was the outcome? Is it resolved, ongoing or did the subject die?
    g. Based on this event, will additional monitoring of other patients be performed in the study to detect similar problems early? If yes, please describe.
    h. Are the possibility, severity and specificity of this event described in the consent form, protocol, and investigator brochure for this study?
    i. Will the consent procedures be revised as a result of this event? If yes, attach the new version of the consent form.
    j. Will patients already enrolled in the study be informed about the possibility of this adverse event? If yes, how?
    k. Name and date of individual submitting the report.

3. Clinical detail should also be made available to the IRB for review; such detail may include the following:
    a. Title of protocol, IRB #, IND or IDE number, Sponsor.
    b. Name of drug/device/procedure.
    c. Medication details, if applicable.
    d. Device parameters, if applicable.
    e. Procedure report, if applicable.
    f. Duration of therapy and dates of administration.
    g. Date of onset and time.
    h. Clinical description of events including signs and symptoms, diagnostic tests performed surrounding event with dates and times.
    i. Treatment initiated for the event.
    j. Outcome of the event.
    k. Has this type of event been reported before?
    l. Could it occur again? This patient or others?
    m. Time frame related to treatment, within 30 days, more than thirty days after treatment began more than thirty days after treatment stopped.

IRBs are responsible for ensuring that reports of unanticipated problems involving risks to human subjects or others are reported to the appropriate government agency. This reporting may be accomplished by the investigator or sponsor reporting the event provided the IRB has documentation of the reporting. Such reporting requirement must be included in PI orientation and approval letters. Events occurring to federally-funded research human subjects must be

reported in accordance with the Terms of Assurance that can be accessed at http://www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm.

The IRB meeting minutes must clearly reflect the comprehensive review of adverse events (specifically Serious Adverse Events), list data analyzed or considered, reflect discussions and approval vote or other actions taken. The IRB must analyze all events from all available sources, such as local patient events and the safety monitoring reports from the sponsors, in aggregate to determine the safety of the protocol.

SAEs Involving a Death, Life-Threatening Event, or Serious Breach of Human Participant Protections

The IRB Administrator will immediately inform the IRB Chairperson, of any SAEs involving any unanticipated death, unanticipated life-threatening event, or serious breach of human participant protections. The IRB Chairperson may decide to call a special IRB meeting to review the SAE and determine whether to modify the protocol and/or the consent form, suspend the study, or take other appropriate action. The IRB Chairperson or IRB Administrator will contact the VP of Quality and Risk Management to inform the Board of Directors and they will decide whether to notify all Board members prior to the next scheduled meeting.

Routine Reports of SAEs

The IRB Administrator will report a summary of SAEs and any related actions to the Facility Director of Quality on a monthly basis.

Reporting Requirements to External Agencies

In accordance with 45 CFR 46.103(a) and 46.103(b)(5), the IRB Administrator will ensure prompt reporting of the following to the IRB, Vice President of Quality and Risk Management and Institutional Official:

(1) Any unanticipated problems involving risks to participants or others,
(2) Any serious or continuing noncompliance with the Federal regulations (45 CFR 46) for the protection of human subjects, or the requirements, and determinations of the IRB, and
(3) Any suspension or termination of IRB approval.

Institutional Official will report the three aforementioned events and all unanticipated deaths that have been determined to be possibly, probably, or definitely study related (categories 3, 4, and 5) to HCA Midwest Division's Board of Directors, the OHRP, and the FDA (if appropriate).

IRB staff will send correspondence, which fulfills HCA Midwest Division's external reporting requirements via Federal Express, United Parcel Service, or another similar overnight carrier which can track the report and verify receipt of the documents.

Additional Adverse Event Reporting Requirements

Principal investigators are also responsible for reporting the following to the IRB in a timely fashion.

(1) New information that may impact the risk/benefit ratio of a study: This may include research findings from other studies, new information in the literature, new FDA labeling and alerts

(www.fda.gov/cder), etc. After careful review, the IRB may recommend that the PI revise the consent form and/or protocol, or change the approval status of the study or the time-frame for continuing review.

(2) Irregularities in conducting the study: Examples include study enrollment prior to obtaining informed consent, improper recruitment (e.g., through coercion), protocol changes implemented without IRB approval, administering a study medication prior to obtaining written consent, administering incorrect dosage of study medication (regardless of injury), and the improper use of study equipment or devices (regardless of any injury).

(3) Data and Safety Monitoring Board reports: as soon as they are available.

(4) Copies of all external SAEs: sent to the PI from the sponsor or other Principal investigators for multi-site studies.

Unanticipated Problems (UP) Reporting Requirement

Only a small subset of adverse events occurring in human subjects participating in research will meet the three criteria for an unanticipated problem (UP). Unanticipated problems, in general, include any incident, experience, or outcome that meets **all** the following criteria:

a. unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent documents; and the characteristics of the subject population being studied;

b. related or possibly related to participation in the research, meaning that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research:

c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) that was previously known or recognized.

Examples of unexpected problems under this definition include the following:

(1) Liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an *unexpected problem*, IF the protocol-related documents did not identify liver disease as a potential adverse event.

(2) Hodgkin's disease (HD) occurring in a subject without predisposing risk factors for HD would be an *unexpected problem* (by virtue of its unexpected nature) IF the protocol-related documents and other reliant sources of information only referred to acute myelogenous leukemia as a potential adverse event.

The reporting requirements for UPs are the same as for SAEs. If adverse consequences or unexpected side effects are encountered in the course of the study, or new information becomes available which could change the perception of a favorable risk/benefit ratio, the Principal investigator is responsible for informing the IRB PROMPTLY. Based on this information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

Principal investigators must report UPs to the IRB within 48 hours of discovery, and 24 hours for deaths. For studies that have been determined by the IRB to be greater than minimal risk, these reports should be filed regardless of whether the UP appears to be study related or is anticipated. For

minimal risk studies, Principal investigators must report only UPs that they believe are probably or definitely study-related. It is the IRB's responsibility (not the Principal investigator's) to determine which studies are classified as minimal risk. Follow up reports and a final written report should be sent to the IRB as soon as the Principal investigator receives additional information regarding the event.

A UP is one of the following events that may occur to a participant during a study:
(1) Death, or a life-threatening event,
(2) Hospitalization or prolongation of hospitalization,
(3) Persistent or significant disability or incapacity,
(4) Birth defect or congenital malformation,
(5) Represents, in the PI's judgment, other significant hazards, or potentially serious harm to research participants or others, or
(6) Any other event as defined in the research protocol.

The IRB Administrator will forward copies of the UP's to the IRB Chairperson/designee for immediate review. If the IRB Chairperson/designee will review the UPs and may ask for additional information from the Principal investigators, such as hospital records, death certificates, pathology or autopsy reports, or request that it be reviewed by another reviewer, if necessary. The IRB Chairperson/designee will determine, to the best of his/her abilities, whether the UPs relationship to the study is unknown, probably related, possibly related, and unlikely related, or not related. S/he will also make recommendations to the IRB regarding if protocol or consent form changes are necessary; and if so, what they are.

The IRB Administrator will contact the Principal investigator if the reviewer requires more information, or if s/he is requesting any protocol or consent form changes.

At each convened meeting, the IRB reviews all new SAE/UP that have been reported since the last convened meeting. If protocol or consent form changes have been recommended by either the Principal investigator or the Chairperson/designee, the IRB will make the decision to accept/reject these proposed changes or to require new ones. The IRB may require more frequent review to monitor the protocol. In rare instances it may become obvious to the Chairperson and the Board that a study carries an unacceptable, unanticipated risk, and the Principal investigator may be asked voluntarily to suspend the study, if he or she has not already done so, pending its re-evaluation. If the problem is deemed of sufficient magnitude, the IRB will direct the IRB Office to promptly report the injury or unanticipated problem involving risks to subjects to the appropriate institutional officials, OHRP, and any other sponsoring Federal department or agency.

Unanticipated Problems Involving a Death, Life-Threatening Event, or Serious Breach of Human Participant Protections

The IRB Administrator will immediately inform the IRB Chairperson, of any UPs involving a death, life-threatening event, or serious breach of human participant protections. The IRB Chairperson may decide to call a special IRB meeting to review the UP and determine whether to modify the protocol and/or the consent form, suspend the study, or take other appropriate action. The IRB Chairperson or IRB Administrator will contact the VP of Quality and Risk Management to inform the Board of Directors and they will decide whether to notify all Board members prior to the next scheduled meeting.

Routine Reports of SAEs/UPs

The IRB Administrator will report a summary of UPs and any related actions to the Facility Director of Quality on a monthly basis.

Reporting Requirements to External Agencies

In accordance with 45 CFR 46.103(a) and 46.103(b)(5), the IRB Administrator will ensure prompt reporting of the following to the IRB and HCA Midwest Division's Institutional Official:

(4) Any unanticipated problems involving risks to participants or others,
(5) Any serious or continuing noncompliance with the Federal regulations (45 CFR 46) for the protection of human subjects, or the requirements, and determinations of the IRB, and
(6) Any suspension or termination of IRB approval.

D. SIGNIFICANT NEW FINDINGS

During the course of a study, the IRB may review reports generated from a Data and Safety Monitoring Board (DSMB), adverse event reports, current literature, and other sources to ascertain the status of the study and assess whether or not the risk/benefit balance is still acceptable. The IRB will review the information to determine whether or not new information needs to be conveyed to subjects, or if a segment of the population may be bearing an undue burden of research risk or being denied access to promising therapy.

E. PROTOCOL DEVIATIONS

The IRB will review the following:

(1) The deviation's net effect on risk,
(2) Why the deviation occurred,
(3) What is being done to prevent future occurrences,
(4) Whether participants were adversely affected by the deviation,
(5) Whether the participants were or should be informed of the deviation,
(6) Whether the deviation indicates additional risks for subjects,
(7) Whether it alter the risk/benefit ratio of the study, and
(8) Whether study or consent procedures are revised accordingly.

The IRB may note the occurrence of the deviation and the Principal investigator's report of it, request more information, request protocol or consent form changes, or suspend enrollment or interaction with subjects if it believes that it is in the best interest of the subjects.

F. RESPONSIBILITY

IRB Administrators and Chairperson (or designee) is responsible for preliminary assessments of modifications or addenda to the protocol or consent form, adverse events, significant new findings, and protocol deviations. IRB Members are responsible for reviewing these reports and determining their affect on human subjects and whether study or consent procedures should be revised accordingly.

G. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.108, 56.109, 56.113
45 CFR 46.103, 46.109, 46.115
FDA Information Sheets, 1998

XI. CONTINUING REVIEW OF RESEARCH

A. POLICY

The IRB conducts continuing review of research taking place within its jurisdiction at intervals appropriate to the degree of risk, but not less than once per year. Generally, at HCA Midwest Division most 'minimal risk' studies are reviewed once a year, and most 'greater than minimal risk studies' are reviewed every six months. The study's risk level and review period will be noted in the original IRB approval letter. Each study must be reviewed at a frequency proportionate to its risks but not to exceed annually. Although the IRB can re-review research at any time, particularly in the presence of new information pertaining to the risk/benefit ratio, at the time continuing review is due, the IRB has the scheduled opportunity to continue approval for a set time period not to exceed 365 days

The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:

(1) Involvement of vulnerable populations;
(2) Research conducted internationally;
(3) Use of waiver of informed consent procedures, (e.g. surrogate consent);
(4) Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of adverse events; and
(5) Previous Administrative Holds or Suspensions of the research due to compliance, record-keeping or other concerns.

Although the IRB Administrator will send out reminder notices when continuing reviews are due, it is the ultimate responsibility of the Principal investigator to submit progress reports to the IRB. Therefore, the Principal investigator should not depend solely on IRB notification as a prompting for submitting all required information.

Continuing IRB review is required as long as individually identifiable follow-up data are being collected or analyzed. This remains the case even after a protocol has been closed at all sites and protocol-related treatment has been completed for all subjects. These renewal requests may qualify for expedited review.

Lapse in Continuing Review:

In the event the review exceeds the IRB approval time frame (regardless of the reason which would include inability of the IRB to review the research timely), the research must stop, unless the IRB finds that it is in the best interest of the individual subjects to continue to participate in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval until the IRB has reviewed the research and approved its continuance.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically and will be ADMINISTRATIVELY SUSPENDED. Such expiration of IRB approval does not need to be reported to the OHRP as a suspension of IRB approval under DHHS regulations.

The continuation of research after expiration of IRB approval is a violation of federal regulations [45

CFR 46.103(a) and 21CFR 56.103(a)]. Once it has been administratively suspended, all research activity on this protocol must stop and no new subjects may be enrolled in the study. Only upon receipt of a formal letter to the IRB requesting reactivation and submission of a completed Progress Report will the renewal of approval process be continued. After approval is granted at a convened meeting of the IRB, the use of that protocol may be continued.

B. DETERMINATION OF THE CONTINUING REVIEW DATE

The following are several scenarios for determining the date of continuing review for protocols reviewed by the IRB at a convened meeting. (These examples presume the IRB has determined that it will conduct continuing review no sooner than within 1 year).

- Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on October 1, 2002. Continuing review must occur within 1 year of the date of the meeting, that is, by October 1, 2003.

- Scenario 2: The IRB reviews a protocol at a convened meeting on October 1, 2002, and approves the protocol contingent on specific minor conditions the IRB Chairperson or his/her designee can verify. On October 31, 2002, the IRB Chairperson or designee confirms that the required minor changes were made. Continuing review must occur within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the protocol, that is, by October 1, 2003.

- Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2002, and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings on October 15 and October 29, 2002. At their October 29, 2002 meeting, the IRB completes its review and approves the study. Continuing review must occur within 1 year of the date of the convened meeting at which the IRB reviewed and approved the protocol that is for example, by October 29, 2003.

C. EXTENSIONS OF APPROVAL PERIOD

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. Extensions beyond the expiration date will not be granted. If Continuing Review Report forms and other requested progress reports are not received as scheduled, the Principal investigator must suspend the study and study enrollment until reports are reviewed and approved.

However, if the Principal investigator is in communication with the IRB, the Continuing Review Report or other report is forthcoming, and in the opinion of the IRB, subjects participating in such a study would suffer a hardship if medical care were discontinued, appropriate medical care may continue beyond the expiration date for a reasonable amount of time. However, **new subjects cannot be enrolled**. The IRB will address on a case-by-case basis those rare instances where failure to enroll new subjects would seriously jeopardize the safety or well being of an individual. Prospective research data cannot be collected, and no procedures that are only being performed for the purposes of the protocol may be performed until a Continuing Review Report or other progress report is reviewed and approved.

D. IRB CONTINUING REVIEW CONSIDERATIONS

Continuing review must be substantive and meaningful. In performing a continuing review, the IRB will look at an Application for Continuing Review, Progress Report, and List of the Adverse Events over the past year, Previously Approved Protocol and Consent Form.

When considering whether or not to renew a study, the IRB revisits the same criteria used to grant initial approval. Therefore, it is the responsibility of the IRB to determine that:
(1) Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
(2) Selection of subjects continues to be equitable;
(3) Informed consent continues to be appropriately obtained and documented;
(4) Adequate provisions for monitoring the data collected to ensure the safety of the subjects is Provided, when appropriate;
(6) Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, is provided, when appropriate; and
(7) Appropriate safeguards for vulnerable populations are provided.

Additionally, the IRB will address the following, during a continuing review:
(1) Are the numbers of subjects accrued consistent with the IRB approved number?
(2) Do the subject withdrawals indicate a problem with the protocol?
(3) Does the progress report include study amendments and new AE information?
(4) Are the risks and benefits as anticipated in the initial review?
(5) Have any subjects been seriously harmed?
(6) Has the IRB been informed of any unforeseen problems that may have occurred?
(7) Since the last review, is there new risk or benefit information that might affect subjects' willingness to participate in the research?
(8) Are there any new findings/knowledge/AEs that should be reported to subjects?
(9) Does the progress of the research together with any new information indicate that the IRB should impose any new restrictions or relax any restrictions that were previously imposed?
(10) Does the consent form require revision?
(11) Are the procedures agreed upon at the beginning of the research still being used?
(12) Are the procedures for data monitoring adequate?
(13) If a study did not have a DSMB, should one be established?
(14) How often should this study be reviewed by the IRB?

If the IRB determines that it needs verification from sources other than the Principal investigator, that no material changes have occurred since the previous IRB review, the IRB may request an independent assessment of information or data provided in the renewal application. The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:
(1) Protocols randomly selected by the IRB office
(2) Complex protocols involving unusual levels or types of risks to participants;
(3) Protocols conducted by PIs who previously have failed to comply with Federal regulations or the requirements or determinations of the IRB; and/or
(4) Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.

The scope and extent of such an independent assessment is determined on a case-by-case basis. Sources for such outside information could include copies of FDA audits, literature searches, site visits conducted by authorized personnel, reports from subjects or study staff, or a directed audit at the direction of the IRB.

Continuing review of DSMB-monitored clinical trials: When a clinical trial is subject to oversight by a DSMB whose responsibilities include review of adverse events, interim findings and relevant literature (e.g., DSMBs operating in accordance with the National Cancer Institute Policy for Data and Safety Monitoring of Clinical Trials), the IRB may rely on a current statement from the DSMB

indicating that it has reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. However, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its continuing review is substantive and meaningful.

IRB approval for the conduct of a study may be withdrawn if the risks to the subjects are determined to be unreasonably high, for example, more than an expected number of adverse events, unexpected serious adverse events; or evidence that the Principal investigator is not conducting the investigation in compliance with IRB or Institutional guidelines. Such findings may result in more frequent review of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken or the study terminated.

E. IRB CONTINUING REVIEW CONSIDERATIONS: CONSENT FORM

The purpose of this consent review is to continually improve the quality of the documents, ensure that the information is still accurate and complete, and to implement any changes newly required by the IRB.

When the IRB requests that routine changes be made to improve the quality of the consent document, it may only require that new subjects sign the revised consent document. However, in instances where the new consent document provides pertinent new information for all subjects and may affect/relate to the subjects' willingness to continue in the study, it may additionally require that current subjects (or only the ones who may be affected by the new information) be re-consented with the new document. If the IRB determines that the new information is important for all subjects, but it would not affect the subjects' willingness to continue study participation, the IRB may require that all subjects be provided with an information sheet, which provides them with the new information. An example of when an information sheet may be used is to provide subjects with new contact information for the Principal investigator or IRB Chairperson.

F. POSSIBLE OUTCOMES OF CONTINUING REVIEW

As an outcome of continuing review, the IRB may require that the research be modified or halted altogether. The IRB may need to impose special precautions or relax special requirements it had previously imposed on the research protocol.

When the IRB determines that changes are necessary, there are two possible outcomes (if there is not sufficient time to return to the IRB with the requested information before the end of the current approval period):

(1) If the changes involve more than specific consent form issues: The Principal investigator will be sent a NOTICE OF SUSPENSION effective on the expiration date of the prior approval until such time as the requested modifications have been reviewed and approved by the convened IRB.

(2) If only specific consent form changes are required: The Principal investigator will be issued a letter indicating APPROVAL OF RENEWAL AS A FOLLOWUP STUDY. This letter grants approval of the continuation of the research described in the protocol for all currently-active subjects, but suspends the project to the accrual of new subjects until such time as the requested modifications to the consent form have been reviewed and approved by the Chairperson of the

IRB.

In either case, the PRIOR APPROVAL REMAINS VALID until the expiration date originally indicated (only a vote of the full IRB can shorten or revoke prior approval), and the Principal investigator has until that date to secure approval for the requested changes.

G. EXPEDITED REVIEW FOR RENEWAL

A protocol with no major changes and minimal risk classification may be eligible to receive continuing review on an expedited basis. Additionally, a protocol that had no accrual during the previous period, or which has not been awarded funding, or which remains open only to data analysis may be reviewed using an expedited review.

When conducting research under an expedited review procedure, the IRB Chairperson or designated IRB member conducts the review on behalf of the full IRB using the same criteria for renewal as stated in this policy. If the reviewer feels that there has been a change to the risks or benefits, he or she may refer the study to the full IRB for review.

H. DETERMINATIONS

Once the IRB has voted to approve a study, the IRB will again make a risk determination for the study, and then determine the review period.

On occasion, the IRB may also determine that the PI should submit a periodic report prior to the next continuing review due date. Examples of these types of reports include an update regarding recruitment, an update regarding a new procedure, an update after the first subject has been medicated, etc. These types of reports will be requested when the IRB feels that it is necessary to be updated on specific information within a certain time frame, however, it does not deem it necessary to conduct a complete continuing review at this time. When this type of periodic report is requested, it will be stated in the approval letter, along with the due date of the report.

The IRB will also determine the need for verification from outside sources.

If Subparts B, C, or D is applicable to the research, the IRB will once again review the research under the appropriate subpart and determine if the requirements have been satisfied.

I. RESPONSIBILITY

IRB Administrators are responsible for establishing and implementing processes for making research renewal decisions. IRB Reviewers are responsible for conducting a thorough review and making all appropriate approval recommendations for consideration by the IRB.

J. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.108,111
45 CFR 46.111
OPRR Reports 95-01

XII. STUDY CLOSE-OUT

A. POLICY

The completion or termination of the study is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report/notice to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

B. DETERMINING WHEN A PROJECT CAN BE CLOSED

HHS-supported protocols: When individually identifiable follow-up data are no longer being collected on subjects enrolled in an HHS-supported protocol, and analysis that could indicate new information is complete, the study may be closed.

Multi-site industry studies may be closed when the Principal investigator submits his or her final report.

C. COMPLETION REPORTS/FINAL REPORTS

Completion reports should be submitted to the IRB within 30 days after completion or termination of the study. Completion reports should be submitted via the Application for Final Review. With the completed Application for Final Review, the Principal investigator should also submit a final report, and any manuscripts or publications that have emanated from the study.

The IRB Administrator will review all reports of study completion and, if needed, request further information from the Principal investigator to clarify any questions that may arise.

Closed studies will be presented to the IRB at the next meeting, and copies of the Completion Report and supplementary information will be made available to the IRB members.

D. RESPONSIBILITY

IRB Administrators are responsible for ensuring all study completion documentation is received, reviewed, presented to the IRB, and filed appropriately.

E. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.108, 56.109
45 CFR 46.103, 46.109

XIII. IRB COMMUNICATION AND NOTIFICATION

A. INVESTIGATIVE STAFF

1. Policy

It is important that staff, subjects, and other interested parties have a means of communicating information about the conduct of a research project directly to the appropriate institutional

officials. It is vital that IRB members and other officials with responsibility for oversight of research have open and ready access to the highest levels of authority within the institution. The researcher and his/her research staff interact with subjects; therefore it is vital that open and frequent communication with the investigative team be maintained.

2. Principal investigator Notifications

a. Initial submission: The Principal investigator will be notified in writing of the IRB's decision as soon as possible after the meeting (within one week of the approval of the meeting minutes). For expedited reviews, Principal investigators will receive written notification within three days of the review. If the approval is pending upon receipt and review of requested materials or responses from the Principal investigator or Sponsor, the IRB must receive the response within 60 days of the date of notification; however, this period may be extended if the Principal investigator/Sponsor communicates a need for an extension.

b. Renewals and revisions: Principal investigators will be notified in writing as soon as possible as to action taken by the IRB for any continuing reviews or revisions (within one week of the approval of the meeting minutes). For expedited reviews, Principal investigators will receive written notification within three days of the review.

c. Notification of approval: Principal investigators will be notified in writing of the approval and provided with an IRB-approved version of the consent form. The IRB-approved consent form will be dated with the period of approval, and initialed by the Chairperson (or the IRB Administrator for the Chairperson). The Principal investigator will also be provided with a document entitled, "Principles to be followed by Principal investigators," which outlines the responsibilities of the Principal investigator.

d. Disapproval: Correspondence will provide the reason(s) for disapproval and instructions to the Principal investigator for appeal of this decision.

3. Principal investigator Appeal of IRB Action

A Principal investigator may appeal the revisions required by the IRB in the protocol and/or informed consent form. This appeal must be in writing and submitted to the IRB Administrator. Principal investigators may also appeal an IRB decision to disapprove a study. Any such appeal may be in writing or in person and must be reviewed by the full IRB at a convened meeting. If the appeal is denied and the study disapproved, the institution cannot override the IRB's decision.

4. Noncompliance

a. It is the responsibility of the IRB staff and members to act on information or reports received from any source that indicate a study being conducted at any facility under the jurisdiction of the IRB could adversely affect the rights and welfare of research subjects. Reports of non-compliance or adverse situations may be reviewed and investigated by the IRB, or referred to the appropriate HCA Midwest Division authority.

b. Principal investigator noncompliance may often be the result of communication difficulties; therefore the IRB and IRB Administrative Staff will attempt to resolve instances of noncompliance without interrupting the conduct of the study, especially if the rights and welfare of subjects may be jeopardized.

c. However, if it becomes apparent that a Principal investigator is intentionally noncompliant, the IRB, through the IRB Chairperson, will notify the Principal investigator in writing, detailing the alleged noncompliance, specifying corrective action, and stating the consequences. Copies of such correspondence shall also be sent to the Sponsor, the individual's supervisor, and HCA Midwest Division's Institutional Official.

d. Should noncompliance continue appropriate action will be determined at a convened meeting. Action by the IRB can include but is not limited to:

(1) Halting the research until the Principal investigator is in compliance. If the research is halted, OHRP will be notified if the research is funded by a government agency, and FDA will be notified if the research involves an FDA regulated product or agent.
(2) Requiring the Principal investigator to complete a training program.
(3) Barring the Principal investigator from conducting further research.
(4) Any other action deemed appropriate by the IRB.

e. When unapproved research is discovered, the IRB and HCA Midwest Division will act promptly to halt the research, ensure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the Principal investigator's fitness to conduct future human subject research.

f. Serious or continuing noncompliance with federal policies on the protection of human subjects or the policies, procedures or determinations of the IRB will be reported promptly to the appropriate department or agency head for funded proposals, Sponsors if appropriate, and to OHRP and/or FDA as appropriate.

g. The IRB's responsibility is to protect the rights and welfare of research subjects, who could be placed at risk if there is misconduct on the part of a Principal investigator or any member of the investigative team. It is, therefore, the duty of the IRB to be receptive to and act on good faith allegations of misconduct. Allegations of misconduct in science should be referred to the Office of Research Integrity and HCA Midwest Division's Institutional Official for handling under HCA Midwest Division policies.

5. Responsibility

IRB Administrators are responsible for overseeing all IRB communications, and for generating appropriate correspondence in response to IRB meetings and decisions.

6. Applicable Regulations and Guidelines

21 CFR 56.109, 56.113
45 CFR 46.109, 46.113

B. OTHER ENTITIES

1. Policy

The IRB is required by federal regulation and institutional policy to communicate certain actions to other entities that may have an interest in the status of the research being conducted under IRB supervision.

2. Communications to Others

a. The purpose of this policy is to ensure prompt reporting to appropriate Institutional Officials, funding sources, department or agency heads, regulatory agencies (OHRP, FDA) and any other appropriate entity of:

(1) Any unanticipated problems involving risks to human subjects or others
(2) Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB
(3) Any suspension or termination of IRB approval, and
(4) Any research that the IRB cannot approve under the terms of 21 CFR 50.24.

The IRB Administrator will ensure prompt reporting of 1-4 to the IRB and HCA Midwest Division's Vice President of Quality and Risk Management.

The Vice President of Quality and Risk Management will report 1-4 and all deaths that have been determined to be possibly, probably, or definitely study related to HCA Midwest Division's Board of Governors, OHRP, and the FDA (if appropriate).

b. Prospective Emergency Research: If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in 21 CFR 50.24 Exemption from Informed Consent Requirements for Emergency Research, notification of disapproval will be conveyed to the Sponsor as well as the Principal investigator.

c. Device studies: If the IRB determines that a study submitted as a non-significant risk presents significant risk, the IRB must notify the Sponsor, FDA, and the Principal investigator.

d. Unexpected or serious adverse events: The Principal investigator must notify the IRB and other entities as stipulated in the Principal investigator's SOPs.

e. Suspension of a study for cause: The IRB will notify HCA Midwest Division's Institutional Official, FDA (when the study involves an FDA regulated product), and federal Agency Head if the research is federally funded, as appropriate.

f. IRB findings and actions will be reported to the Institutional Official each month by way of the IRB meeting minutes. The IRB Administrator will forward the approved minutes from all IRB meetings, within one week of the meeting, to the Institutional Official.

3. Responsibility

IRB Administrators are responsible for corresponding with other interested entities concerning the status of research under review by the IRB. IRB Chairperson (or designee) is responsible for ensuring appropriate discussion and IRB decision-making regarding un-approvable emergency research, risk assessment of investigational device, adverse event assessments and Principal investigator non-compliance.

4. Applicable Regulations and Guidelines

21 CFR 50.24
21 CFR 56.113

45 CFR 46. 113
21 CFR 812.66

XIV. RESPONSIBILITITES OF PRINCIPAL INVESTIGATORS

IRB-REQUIRED PRINCIPAL INVESTIGATOR ACTIONS

A. Policy

Between IRB initial approval of a protocol and the time of continuing review of a study, it is the Principal investigator's responsibility to keep the IRB informed of unexpected non-serious (only if the study is classified by the IRB as greater than minimal risk) and serious adverse events and other unexpected findings that could affect the risk/benefit ratio of the research. A Principal investigator is responsible for the accurate documentation, investigation and follow-up of all possible study related adverse events. Principal investigators are also responsible for informing government and other Sponsors of any unanticipated or serious adverse events, as appropriate.

B. IRB Review of Research

All human subjects research that is conducted by (or under the direction of) any employee, of HCA Midwest Division, in connection with his or her institutional responsibilities, must be reviewed by the IRB.

C. Informed Consent

The Principal investigator must obtain informed consent from subjects prior to their enrollment into the research. The Principal investigator must use the informed consent document approved by the IRB. Approval and expiration dates are indicated on the consent document. Consent documents are valid only during the dates indicated on the form and/or approval notification; and the Principal investigator may use the forms only during the period for which they are valid.

D. Adverse Event Reporting

The IRB must be informed of any serious, unexpected or alarming adverse events that occur during the approval period. Principal investigators or Sponsors must also submit Sponsor-generated reports of adverse events occurring at other investigative sites.

E. Changes in Approved Research

Changes in approved research, during the period for which approval has already been given, may not be initiated without IRB review (or expedited review, where appropriate) and approval, except where necessary to eliminate apparent immediate hazards to human subjects. Principal investigators or Sponsors must submit requests for changes to the IRB in writing via the Application for Protocol/Consent Form Amendment. Upon receipt of the protocol change, the IRB Chairperson will determine if the revision meets the criteria for minimal risk. If the change represents more than a minimal risk to subjects, it must be reviewed and approved by the IRB. Minor changes involving no more than minimal risk to the subject may be reviewed by the expedited review process.

F. Periodic Reports

The length of time approval is given to a research protocol will be no more than one year, and is dependent on the risk involved with the research. Principal investigators are responsible for requesting renewal in anticipation of the expiration of the approval period. Principal investigators or their designees and/or Sponsors are required to provide a report regarding their investigation prior to the end of the approval period, or upon completion of the study. An IRB Application for Continuing Review will be available to the Principal investigator for this purpose.

On occasion, the IRB will request that the PI submit a periodic report prior to the date of the continuing review. Examples of these types of reports include an update regarding recruitment, an update regarding a new procedure, an update after the first subject has been medicated, etc. When this type of periodic report is requested, it will be stated in the approval letter, along with the due date of the report. It is the responsibility of the Principal investigator to submit this report to the IRB prior to the due date.

G. Conflict of Interest

The protection of human subjects requires objectivity in communicating risks, selecting subjects, promoting informed consent, and gathering, analyzing and reporting data. Therefore, the IRB should consider conflict of interest issues in its deliberations of applications. All Principal investigators must reveal on their application to the IRB whether they or any other person responsible for the design, conduct, or reporting of the research has an economic interest in, or acts as an officer or a director of any outside entity whose financial interests would reasonably appear to be affected by the research.

H. Responsibility

IRB Administrator is responsible for tracking Principal investigator compliance with IRB requirements stipulated during the IRB's review of the Principal investigator's research, and for engaging appropriate Principal investigator sanctions when Principal investigators are not in compliance with IRB requirements. IRB Chairperson (or designee) is responsible for facilitating Principal investigator compliance with IRB requirements through his/her management of IRB deliberations, and providing Principal investigators clear guidelines pertaining to that compliance through IRB communications to the Principal investigator.

With the approval letter, the IRB Administrator will include the document entitled "Principles to be followed by Principal investigators," which outlines the responsibilities of the Principal investigators throughout the IRB approval period.

I. Applicable Regulations and Guidelines

21 CFR 56.109, 56.111
21 CFR 54
45 CFR 46.109, 46.111
Draft Interim Guidance: Financial Relationships in Clinical Research: Issues for Institutions, Clinical Principal investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection, January 10 2001, OHRP, HHS

XV. QUALITY ASSURANCE (QA)

A. QA PROGRAM

1. Policy

Quality assurance and control of the daily operations of the IRB ensure effective support of the IRB's mandate. Therefore, the QA program consists of three components:

(a) Training and continuing education of IRB staff.
(b) Interactions with the IRB community outside the HCA Midwest Division jurisdiction.
(c) Regular review and assessment of procedures.

The IRB has the authority to implement a QA program and to act on identified deficiencies by implementing corrective action via revisions to the Standard Operating Policies and Procedures.

2. Responsibility

The IRB Administrator is responsible for the establishment, implementation and oversight of the QA program.

3. Applicable Regulations and Guidelines

None

B. AUDITS BY REGULATORY AGENCIES

1. Policy

HCA Midwest Division acknowledges that certain regulatory agencies have the authority to audit the operations of the IRB, and support such audits as part of its continuing effort to maintain high standards for human research protections. Entities that may audit IRBs include: FDA, OHRP, JCAHO, and appropriate certified auditors of foreign countries where data from clinical research has been submitted in an application for drug or device approval. Sponsors or funding entities of research may also be authorized to audit specific documents and procedures.

2. Preparing for an Audit

For audits involving OHRP or FDA, the following must be notified immediately:
(1) HCA Midwest Division's Institutional Official
(2) IRB Chairperson
(3) IRB Administrator

Those designated to participate in the audit are required to follow the steps outlined by this institution for preparing the site for an audit.

3. Participating in an Audit

a. IRB staff (and members if applicable) is expected to know and follow the procedures outlined by this Institution for the conduct of a regulatory audit.

b. Prior to being granted access to IRB documentation, inspectors or auditors must exhibit proof of their authority or authorization to conduct the audit and to access IRB documents. No entity other than those listed on the consent forms may have access to any document that includes subject identifiers.

c. Auditors will be provided with adequate working area to conduct an audit and IRB staff and members must make every reasonable effort to be available and to accommodate and expedite the requests of such auditors.

d. Documents may be copied and taken off-site only by individuals authorized in writing by the IRB Chairperson to do so.

4. Follow-up After an Audit

Reports of the audit, either verbal or written, should be addressed by the IRB Administrator in conjunction with the Institutional Official, as soon as possible after the audit.

5. Responsibility

a. The Institutional Official is responsible for serving as the responsible institutional official in all regulatory agency matters regarding regulatory compliance, participating as needed in regulatory agency audits, and providing support in responding to and correcting audit findings. The Institutional Official may delegate or appoint individuals to participate in audits on his/her behalf.

b. The IRB Supervisor and/or Administrator is responsible for all formal regulatory agency correspondence and interactions, establishing logistical support during regulatory agency audits, serving as key institution contact during such audits, and drafting responses to regulatory agency correspondence received following such audits.

c. IRB Chairperson, Members and Staff are responsible for participating in regulatory agency audits as determined by the Administrator, and in fully cooperating with government officials during their participation in such audits.

d. IRB Chairperson is responsible for assisting the IRB Administrator in formal responses to regulatory agency audits and in implementing policy and procedure changes indicated by such audits.

6. Applicable Regulations and Guidelines

21 CFR 56.115
45 CFR 46.115
FDA Compliance Program Guidance Manual 7348.809, Institutional Review Boards