INDEPENDENT
INVESTIGATIONAL
REVIEW BOARD INC.

6738 West Sunrise Boulevard, Suite 102
Plantation, Florida 33313

Human Research Protection Program Plan (HRPP Plan)

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Anita McSharry, President — Date of Approval: 9/17/2009

Kim Lerner, Chief Executive Officer — Date of Approval: 9/17/2009

ABBREVIATIONS

AAHRPP	Association for the Accreditation of Human Research Protection Programs, Inc.
AE	Adverse Event
CDER	Center for Drug Evaluation and Research
CDPR	California Department of Pesticide Regulation
CFR	Code of Federal Regulations
COI	Conflict of Interest
CQIP	Continuous Quality Improvement Program
CRO	Contract Research Organization
DHHS	Department of Human and Health Services
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FR	Federal Regulations
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRP	Human Research Protection
HRPP	Human Research Protection Program
HSRB	Human Studies Review Board
ICH	International Conference on Harmonisation
ICE	Internal Communication Exchange
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IND	Investigational New Drug
IO	Institutional Official
IOAG	Institutional Official Advisory Group
IRB	Institutional Review Board
IIRB, Inc.	Independent Investigational Review Board, Inc.
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
NIH	National Institutes of Health
NSR	Non Significant Risk
OHRP	Office of Human Research Protection
PHI	Personal Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SR	Significant Risk
WI	Work Instruction

1 INDEPENDENT INVESTIGATIONAL REVIEW BOARD, INC.

The Independent Investigational Review Board, Inc. (IIRB, Inc.) is located in offices at 6738 West Sunrise Boulevard, Suite 102, Plantation, Florida 33313 and is equipped with all necessary office space, meeting space, storage space, hardware and software resources and equipment to perform the functions required for the Human Research Protection Plan (HRPP). Office equipment and supplies, including technical support, file cabinets, computers, computer systems, record retention capabilities, document disposal, internet access, and copy/fax/scanner machines, are available to all of the IIRB, Inc. staff and will be reviewed on an annual basis or as additional resources become needed.

The IIRB, Inc. (Organization) is composed of a Board of Directors, Institutional Official (IO), Institutional Official Advisory Group (IOAG), Institutional Review Board (IRB), Qualified Screening Staff, Administrative Staff, and Financial and Human Resource Personnel.

The President of the Organization serves as the signatory official of the IRB registration with OHRP and the FDA (#IRB00003563). The Board of Directors is responsible for granting signatory authority to individuals at IIRB, Inc. and will grant or remove signatory authority from individuals as needed. The President and CEO in unanimous agreement may deem it necessary to appoint an individual to have temporary signatory authority for a given period of time. The President and CEO of the Organization, Chair of the IRB, and Vice Chair have signatory authority for the IRB, and are authorized to sign all documentation from the IRB, including documentation of actions taken by the IRB, Expedited Reviewer, or Administrative Reviewer. By signing such correspondence, these authorized individuals are signing as a representative of the organization and not as the reviewer of the submission for which the correspondence addresses. Separate authorization from the Executive Committee is necessary for individuals to have signatory authority for financial matters.

1.1 MISSION AND PURPOSE OF IIRB, INC.

IIRB Inc. mission and purpose is to protect the rights and welfare of human subjects involved in research, as defined by Federal Regulation. It upholds and adheres to the principles of The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979).

In order to fulfill the mission, the IIRB, Inc has established an Institutional Review Board (IRB) that meets federal regulatory requirements for the review of human subject research. See Institutional Review Board (IRB) section for a more detailed discussion of the IRB.

1.2 BOARD OF DIRECTORS

The Board of Directors is chaired by the President of the IIRB, Inc. The President and Chief Executive Officer of the Organization are executive directors of the Board of Directors and form the Executive Committee. The Board of Directors is responsible for the financial planning and direction of the Organization. The Board of Directors is composed of executive directors who are dedicated full-time to their role in relation to the management of the Organization, and non-executive directors who are approved for their expertise, and to lend an impartial view in relation to strategic decisions and oversight of the Organization. At least

one director will be a member of the IRB who is not otherwise affiliated with the IIRB, Inc. The Executive Committee is responsible for overseeing all financial affairs at the IIRB, Inc. and has signatory authority for the HRPP Plan following approval by the Board of Directors. The Executive Committee will meet annually or on an as necessary basis. The President of the organization prohibits anyone approving research that has not been approved by the IRB.

1.2.1 RESPONSIBILITIES OF THE BOARD OF DIRECTORS

- The Board of Directors is responsible for the review and approval of the HRPP Plan.
- The Board of Directors is responsible for the oversight, quality assurance, and management of all affairs under the IIRB, Inc. including actions taken by the IRB, IOAG members, and Administrative Staff.
- The Board of Directors is responsible for the appointment of the IRB members, Chair and Vice Chair and IO. The appointment will be based on the needs of the organization and regulatory requirements. The qualifications for appointment will be reviewed and adequacy assessed by the Board of Directors.
- The Board of Directors will perform annual performance evaluations of members of the IRB, IRB Chair and Vice Chair, and the IO. The Board of Directors has the authority to reappoint, not reappoint, or to remove any member of the IRB including the Chair or Vice Chair, and also has the authority to reappoint, not reappoint, or to remove the (IO). Removal or non-reappointment will occur if the Board of Directors determines that the IRB member, Chair or Vice Chair or IO has unduly influenced the IRB, has used his or her position and authority to coerce the IRB, has excessive absences, and/or is not performing to the expectations of the Board of Directors or adhering to the policies and procedures of the HRPP Plan. The determination for reappointment will be based on the evaluation of the IRB member's, Chair's, Vice Chair's or IO's overall performance.
    - To remove a member of the IRB, Chair or Vice Chair or IO, the Board of Directors must meet in its entirety and a majority must agree that the removal of the IRB member, Chair or Vice Chair or IO is warranted.
- The Board of Directors will perform an annual assessment of the adequacy of the number of IRBs and the performance of the current IRB. The IO will report regarding the adequacy of the number of IRBs based on the organization's needs and key indicators included in the CQIP Plan (Attachment 8).

1.2.2 BOARD OF DIRECTORS MEETING

The Board of Directors will meet at least twice in a calendar year to discuss activities of the IIRB, Inc. including overall business practices, review of policies and procedures, evaluation of the Human Research Protection Program Plan (HRPP Plan) and review of quality assurance reports. In addition, the Board of Directors will appoint members to the IRB including a Chair on an annual basis or as warranted.

1.2.3 REPORTS OF UNDUE INFLUENCE

The Board of Directors is responsible for the resolution of any reports of undue influence reported as concerns of the staff, IRB members, Investigators, or Sponsors/CRO. All concerns will be brought to the individual(s) in Human Resource services or the IO, as

applicable. This individual will evaluate the concern to determine if the concern is due to undue influence. If the event does not involve the President or CEO, the President who serves as the IO will be notified. If the event involves the President or CEO, a member of the IOAG (without equity interest) will be notified of the reported concern. In the event that the concern involves the President and/or the CEO, the member of the IOAG (without equity interest) will bring this concern to the IOAG and the President and/or CEO will recuse themselves from the IOAG meeting. The IOAG will evaluate the reported concern, and determine if notification to the Board of Directors is warranted. If the concern warrants reporting to the Board of Directors, the Chair or designee will contact a member of the Board of Directors other than the President and CEO with this concern. The Board of Directors may determine that an individual be removed from the IRB, employment terminated, or that future research studies be denied review. The IRB member, employee, Investigator, or Sponsor/CRO can request an appeal of this decision by contacting the Board of Directors verbally or in writing. The Board of Directors will review the reports of undue influence, and determine if further action is required. The individual requesting an appeal will be notified of the Board of Director's findings.

1.3 INSTITUTIONAL OFFICIAL

The President of the Organization also serves as the Institutional Official (IO) and is identified as accountable for the IIRB, Inc. HRPP Plan. The IO is legally authorized to represent the Organization and reports to the Board of Directors.

The IO is the point of contact for correspondence addressing human research with the DHHS Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA) and any other federal regulatory agencies.

The IO also holds oversight of the IRB and is responsible for assuring the IRB members and IIRB, Inc. staff are appropriately knowledgeable. The IO ensures that investigators who are conducting research under the umbrella of IIRB, Inc. are conducting research in accordance with ethical standards and applicable regulations. The IO oversees the development and implementation of an educational plan for IRB members and staff and assures the educational status of investigators.

The IO cannot overrule ANY research study-related action of the IRB. If the IO determines that the IRB decision regarding research is not consistent with the HRPP Plan or with regulatory guidelines, the matter will be further addressed by the IRB and IO jointly and a review of the HRPP Plan and appropriate regulatory guidelines will be performed so that resolution consistent with regulatory guidelines is accomplished. Resolution of these controverted issues will be reported to the Board of Directors.

In addition, the IO serves as the Chair of the Institutional Organization Advisory Group (IOAG) and is responsible for:

1. Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing all aspects of the HRPP Plan.

2. Implementing the organization's HRPP Plan.
3. Submitting, implementing and maintaining IRB registration with the Department of Health and Human Services Office of Human Research Protection (OHRP).
4. Assisting investigators in their efforts to carry out their research mission.
5. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risks in the research program.
6. Developing training requirements as necessary and as appropriate for Investigators, IRB members and research staff, and ensuring that training is completed on a timely basis.
7. Ensuring that actions carried out by "Expedited Review Procedures" are consistent with this HRPP Plan.
8. Evaluating and assessing the functions of the IRB, the appropriate number of IRBs, HRPP Plan, participant outreach, the performance and concerns of IRB Members, IOAG members, Qualified Screening Staff, and Administrative Staff, and the adequacy of resources (i.e., office space, supplies, computer systems, and trained staff) provided to conduct business.
9. Working in cooperation with the IRB Members, IOAG members, Qualified Screening Staff, Administrative Staff and Consultants to provide a venue to express their concerns, suggestions, or any allegation of coercion or undue influence. These areas of concern can be reported to the IO, at any time, by email, telephone, facsimile, or face to face conversations. The IO will present these concerns in a timely manner to the IOAG and Board of Directors based on the potential significance of the report. Individuals that present allegation of coercion or undue influence will be not be penalized and are encouraged to bring forward any concerns. The Board of Directors will take these allegations seriously and will investigate and take action as appropriate. If a Sponsor or CRO has been deemed to have potentially acted in an inappropriate manner the future review of research studies or termination of research will be considered.
10. The IO is responsible for reporting significant findings of the above mentioned areas to the Board of Directors as necessary.

The IO may delegate duties to specific IRB Members, IOAG members, Qualified Screening Staff, or Administrative Staff however, the IO is ultimately responsible for the oversight of these duties. The IO may decline review of a research study for any reason.

1.4 INSTITUTIONAL OFFICIAL ADVISORY GROUP (IOAG)

The IOAG is an advisory committee to the IO and is comprised of members of the Organization and Board of Directors (see organizational chart and job descriptions for members from the IIRB, Inc.). The IOAG is governed by the directives of the HRPP Plan but is not limited exclusively to HRPP matters. The IOAG addresses other areas of Organizational Management as directed by the Board of Directors. The purpose of the IOAG is to provide a mechanism for day-to-day operational guidance and direction for the Organization. The IOAG is intended to include additional leadership in the oversight of the IIRB, Inc. and includes individuals that do not have an "ownership" interest in the organization.

The IOAG reports to the Board of Directors as necessary and provides direction and feedback to the IRB and staff.

1.5 QUALIFIED SCREENING STAFF

Qualified Screening Staff are a select group of individuals within the organization that have demonstrated experience in IRB related procedures as well as the procedures outlined in this HRPP Plan. Qualified Screening Staff may not have equity interest in the IIRB, Inc. The activities that Qualified Screening Staff may engage in vary according to level of expertise and are documented in their respective Training and Education File.

1.6 ADMINISTRATIVE STAFF

Administrative Staff members include Project Leaders (i.e., including Assistant, Senior, and all Levels), and other supporting staff members (see Organizational Chart for more details). Administrative Staff are responsible for providing administrative and clerical support to the President, IO, CEO, IRB Chair, Vice Chair, IOAG members, Qualified Screening Staff, and Administrative Staff are responsible for activities outlined in their job descriptions which may include overall routine management of multiple projects to include preparation, maintenance and administrative duties of client files from document submission to completion of IRB action. Responsibilities also include proactive communication between Investigators, Sponsors/CROs and IIRB, Inc. to ensure effective support and delivery of HRPP Plan objectives. Administrative Staff members are qualified to perform the tasks listed in this document based on their qualifications listed in their individual training files and by meeting the qualifications for each given position listed on their respective Job Descriptions.

Administrative Staff are evaluated on at least an annual basis by the IO and CEO on overall performance and compliance with HRPP Plan. Administrative Staff are under the supervision of the IO of the IIRB, Inc.

1.7 LEGAL COUNSEL

The HRPP Plan and the IRB rely on Legal Counsel for the interpretation and application of Florida State law and the laws of any other jurisdiction where research is conducted as they apply to human subject research. Legal Counsel will assist the IRB in determining whether an individual or class of individuals meet the definitions for "legally authorized representative, "child/children," and "guardian," who under applicable law is authorized to consent on behalf of another person to undergo procedures in a research study, and who under applicable law has reached the legal age to consent to the treatments or procedures in a research study (including analysis of the legal status of subject i.e. emancipation or marital status).

Legal Counsel will provide counsel on other laws when they are relevant to the research context, such as: additional protections for humans involved in research, additional protections for vulnerable populations involved in research, educational services, genetic testing, HIV testing, informed consent, limitations of waiver of informed consent, mandatory reporting of abuse, mandatory disease reporting, mental health services, medical records, and privacy and confidentiality. All consent forms must be consistent with applicable state and local laws.

2 HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

In order to fulfill the mission of IIRB, Inc., the organization has established a Human Research Protections Program (HRPP). The mission of the HRPP is to safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected, by providing timely and high quality education, by reviewing and monitoring of human research projects, and by facilitating excellence in human subject research. The objective of this system is to direct and oversee the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The HRPP is a multi-tiered program involving the Board of Directors, IRB, IOAG, Qualified Screening Staff and Administrative staff. The HRPP includes mechanisms to establish a formal process to monitor, evaluate and continually improve the protection of human research participants, dedicate sufficient resources, exercise oversight of research protection, educate Investigators and research staff about their ethical responsibility to protect research participants, and when appropriate, intervene in research and respond directly to concerns of research participants.

The HRPP (including attachments) is part of the HRPP Plan and is reviewed and approved by the Board of Directors on an annual basis, with review from the IOAG and IRB as necessary. IRB Members will document their review of the HRPP Plan on the Board Training and Education Form or IRB Meeting Minutes as appropriate.

The attachments to the HRPP Plan can be revised by the IO or designee on an as needed basis, provided that the changes are consistent with the HRPP. The IO can revise sections of the HRPP Plan at any time he/she determines that changes must be implemented immediately in order to be compliant with operations and the remainder of the HRPP Plan. These immediate changes will be reported to the IRB and IOAG, and will be incorporated in the currently approved version of the HRPP Plan. These changes will be approved by the Executive Committee. The Board of Directors at their next regularly scheduled meeting will review these changes and either approve, disprove, or alter the revisions made by the IO. Changes to the HRPP Plan do not need to be reviewed by the IRB, if the changes are typographical or formatting changes, minor clarifications, or changes that do not directly affect the role of the IRB.

The HRPP includes the Plans that are identified and described herein.

2.1 ORGANIZATIONAL CHART AND PLAN

The Organizational Chart provides an overview of the IIRB, Inc. reporting structure. The Organizational Chart identifies the relationships between the Board of Directors, IO, IOAG, IRB, Administrative Staff, and Financial and Human Resource Personnel (Attachment 1 – Organizational Chart and Plan).

2.2 CONFLICT OF INTEREST PLAN (INTERNAL AND EXTERNAL)

The Conflict of Interest Plan includes the process to identify, manage, report and maintain information regarding potential and identified conflicts of interest. The Conflict of Interest

Plan (COI Plan) includes potential and identified conflicts reported by individuals within the IIRB, Inc. organization, IRB Members, IRB Consultants, investigators and key research staff involved in research that is under the oversight of the IIRB, Inc. The COI Plan will ensure that prospective investigators are aware of IIRB's definitions and thresholds for "conflicts of interest" and "significant financial interests" by providing this information on the IIRB, Inc. website and by identifying them in the Investigator's Guidebook. In addition, the COI Plan will ensure that IRB Members and Consultants have an awareness and understanding of what a COI entails and the processes involved. This will be conducted by providing COI in-house training to the IRB Members and Consultants, and by discussing potential COI at every IRB Meeting (Attachment 2 - Conflict of Interest Plan - Internal and External).

2.3 SITE EVALUATION PLAN

The purpose of the Site Evaluation Plan is to provide the IRB with a mechanism to conduct initial and ongoing Site evaluation process. The Site Questionnaire is the primary tool for implementing the Site Evaluation Plan and provides information about site staff training, knowledge, equipment and qualifications to determine the competence of the Investigator to conduct the submitted research study. The Site Questionnaire provides the IRB with information about a site's consenting process, recruitment methods, and provisions to protect the rights and welfare of potential research subjects. The Site Questionnaire is intended to integrate the Site Evaluation Plan with the Research Evaluation Process and Plan (Attachment 3 – Site Evaluation Plan).

2.4 RESEARCH EVALUATION PROCESS AND PLAN

All research under the oversight of the IIRB, Inc. will be evaluated through the research evaluation process. The research evaluation process begins with the information provided by the Site and culminates with the action of the IRB. At any time during this process additional information or modifications may be required. All findings are documented in the Research File and in the minutes of the IRB. The purpose of this process is to ensure that the site and research study meet the criteria for approval, that elements are in place to protect the rights and welfare of the subjects, and to provide guidance to the IRB or expedited reviewers in reviewing submissions and taking action (Attachment 4- Research Evaluation Process and Plan).

2.5 IIRB, INC. WEBSITE OVERVIEW

The purpose of the IIRB, Inc. Website Overview is to serve as a synopsis, purpose, and rationale of each aspect of information that is contained in the www.iirb.com website (Attachment 5- IIRB, Inc. Website Overview).

2.6 INVESTIGATOR'S GUIDEBOOK

The purpose of the Investigator's Guidebook is to serve as a compliance tool for investigators to utilize when conducting research under the oversight of the IIRB, Inc. In addition, the Investigator's Guidebook also provides guidance and education to Investigators conducting research studies involving humans (Attachment 6- Investigator's Guidebook).

2.7 IRB MEMBERSHIP DOCUMENTATION PLAN

The IRB Membership Roster documents IRB member roles and qualifications. The roster presents an overview of the IRB Membership expertise. The IRB Membership Roster is posted on the website. A summary is maintained that documents compliance with AAHRPP requirements and includes the names of IRB members, earned degrees, scientific status, representative capacity, indications of experience, relationship of the member to the organization, affiliation status, office, membership status, and alternate status. The IRB rosters also include the primary members or class of primary members for whom each alternate member can substitute (Attachment 7-IRB Membership Documentation Plan).

2.8 CONTINUOUS QUALITY IMPROVEMENT PROGRAM (CQIP) PLAN

The HRPP Plan includes identifying opportunities to maximize compliance with IIRB, Inc. policies and procedures and provides opportunities for continuous quality improvement. The CQIP is intended to ensure the HRPP plan and the efforts made by the Organization, IRB, and Investigators under the oversight of the IIRB, Inc. are performed in such a way to meet the goals of the HRPP Plan and to provide optimal human research protection. In addition, the CQIP Plan includes information on internal and external site audits and visits (Attachment 8- Continuous Quality Improvement Program (CQIP) Plan).

2.9 TRAINING AND EDUCATION PROGRAM PLAN

The purpose of the Training and Education Program Plan is to provide training as an on-going educational process related to ethical concerns and regulatory and institutional requirements for the protection of human subjects. The Training and Education program is intended to ensure compliance with the HRPP Plan and Organization's Mission (Attachment 9-Training and Education Program Plan).

2.10 INFORMED CONSENT PROCESS AND DOCUMENTATION PLAN

The purpose of the Informed Consent Process and Documentation Plan is to provide guidance for the IRB and for Investigators to comply with the requirements that informed consent is sought from each subject or Legally Authorized Representative (LAR) and is appropriately documented. It includes the primary elements of the informed consent process and documentation, and integrates with the Site Evaluation Plan and the Research Evaluation Process and Plan (Attachment 10-Informed Consent Process and Documentation Plan).

2.11 RESEARCH PARTICIPANT OUTREACH PLAN

The purpose of the Research Participant Outreach Program Plan is to provide an overview of the Research Participant Outreach Program. The Plan includes systematic mechanisms for implementing the Research Participant Outreach Program Plan and for evaluating its effectiveness for ensuring educational opportunities are offered to research participants, prospective research participants, and community members to enhance their understanding of research involving human participants conducted under its oversight (Attachment 11-Participant Outreach Program Plan).

2.12 VULNERABLE POPULATION PROTECTION PLAN

The purpose of the Vulnerable Population Protection Plan is to identify those populations that are potentially vulnerable to coercion or undue influence, to identify additional safeguards to protect the rights and welfare of these subjects, to ensure sites have processes in place to protect the rights and welfare of the vulnerable populations, and to provide guidance to the IRB in reviewing submissions and taking action (Attachment 12- Vulnerable Population Protection Plan).

2.13 DOCUMENT DISTRIBUTION PLAN

The purpose of the Document Distribution Plan is to identify the timeframe and method of distributing research related documents to IRB Members to ensure adequate review prior to a scheduled IRB meeting (Attachment 13- Document Distribution Plan).

2.14 INTERNATIONAL RESEARCH EVALUATION PLAN

The purpose of the International Research Evaluation Plan is to identify the additional considerations that are given to research that will conducted outside the U.S. in regards to medical qualifications, assessment of site mores, and IRB/IEC requirements (Attachment 14 –International Research Evaluation Plan).

2.15 DISASTER PLAN

The purpose of the Disaster Plan is to identify the actions necessary to prepare the facility for a natural disaster including but not limited to a hurricane, tornado, flood, or any other relevant disaster applicable to the location of the IIRB, Inc. organization in order to minimize damage to property, maintain confidentiality of data, and to provide for the continuity of service (Attachment 15 – Disaster Plan).

2.16 DATA SECURITY PLAN

The purpose of the Data Security Plan is to identify the systems used by the Independent Investigational Review Board, Inc. (IIRB, Inc.) to collect, store, transmit, and maintain data pertinent to the functions of the organization and to fulfill the requirements listed in the Human Research Protection Program Plan (HRPP Plan) (Attachment 16 – Data Security Plan).

2.17 COMPILATION OF OTHER FORMS

Forms not specifically identified as attachments to this plan are separately maintained in the IIRB, Inc. Forms manual.

3 INSTITUTIONAL REVIEW BOARD (IRB)

IIRB, Inc. currently has one IRB, appointed by the Board of Directors. The IRB reviews research activities including but not limited to; Phase I, II, III or IV or Device studies (as defined by FDA regulations) and research regulated by the EPA. The IRB is in compliance with both the regulations of the Food and Drug Administration contained in the Code of Federal Regulations (2I CFR 50 and 56) and in accordance with regulations described in 45 CFR 46, Department of Health and Human Services (DHHS). The IRB will review studies

regulated by the Environmental Protection Agency (EPA) within the scope of regulations included in 40 CFR Parts 9 and 26, Protections for Subjects in Human Research, and Final Rule. In addition, ICH/GCP guidelines are observed and review is conducted in compliance with 45 CFR Parts 160 and 164, the Privacy Rule, and the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the review of research involving human subjects conducted by DHHS or supported in whole or in part by DHHS, and review of research regulated by the EPA involving human subjects where the FDA, EPA regulations and the DHHS Regulations apply, the more stringent requirements will be met.

The IRB is responsible for the process of protecting the rights and welfare of human research subjects in research conducted under the oversight of the IIRB, Inc. The IRB conducts all of the Investigational Review Board required review functions as defined in regulatory guidelines. It discharges this duty by complying with the requirements of state regulations, federal regulations and IIRB, Inc. policies.

The Board of Directors, IO, IOAG, Qualified Screening Staff, or any other employee of the IIRB, Inc. may not approve the research if it has been disapproved by the IRB. Previously approved research proposals and/or consent forms by another IRB must be re-approved by the IIRB, Inc's IRB before initiation and will be handled in the same manner as any proposed research.

3.1 IRB COMPOSITION

All members of the IRB shall follow the membership guidelines established in 21 CFR Subpart 56.107, 45 CFR 46.107, and 40 CFR 26.107.

An IRB Membership Roster is maintained and will include information to reflect the education and background of each member. A current version of the IRB Membership Roster is located on the IIRB, Inc. website. A file will be kept that includes the curriculum vitae, licenses and certifications (as warranted), Confidentiality Agreements, Internal Conflict of Interest and Disclosure Forms, IRB Training and Education Form documents, Collaborative Institutional Training Initiative (CITI) completion reports, and any other HRP training documentation. These files will be updated and maintained by a Qualified Screening Staff or designee.

3.2 APPOINTMENT OF IRB MEMBERS

The Board of Directors shall appoint all members (including alternates). The Vice Chair is empowered to act as IRB Chair in the absence of the IRB Chair or in the event that the Chair and Vice Chair have agreed that the Vice Chair will serve as the Chair of a given meeting. The IRB member's length of term is one year and may be extended without limit based on the authority of the Board of Directors. The IO and CEO in conjunction with the Chair may determine an immediate need for appointment of an IRB Member. Such instances can include events such as unexpected resignation, leave of absence, death, or immediate need of additional expertise. The IO and CEO in conjunction with the Chair will interview a potential IRB Member and allow the IRB to vote on adding the new IRB Member with the contingency that the new IRB Member must be fully reviewed and appointed at the next Board of Directors meeting.

Each member, including the Chair and Vice Chair, will each have one vote. Members will

have designated Alternates appointed by the Board of Directors. The Alternate will serve in a similar capacity as the member and will attend meetings as needed and may be invited to attend to maintain current competence without vote. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

3.3 IRB MEMBER, CHAIR AND VICE CHAIR RESPONSIBILITIES

All IRB Members including the Chair and Vice Chair are required to sign an IRB Member Job Description that outlines the responsibilities and expectations of serving as IRB Members. In addition, the responsibilities of the Chair and Vice Chair include member responsibilities and conduct of the meeting in accordance with Robert's Rules of Order.

3.4 IRB COMPLIANCE

The IRB shall follow the HRPP Plan and will review the Plan on at least an annual basis.

3.5 IRB CONFIDENTIALITY

Members of the IRB agree to keep confidential all proprietary information and will not disclose or divulge confidential information. All IRB Members and Consultants are required to sign a Confidentiality Agreement on an annual basis.

3.6 MEETING SCHEDULE/FREQUENCY

Meetings are scheduled on a weekly basis, and meetings may be scheduled more frequently as needed. Prior to the scheduling of an additional meeting, the Chair/Vice Chair will obtain confirmation of member attendance to assure that a Quorum will be present.

3.6.1 IRB MEETING CALENDAR

The purpose of the IRB Meeting Calendar is to provide Sponsors, CROs, and Investigators with a schedule of upcoming IRB meetings and deadlines for submitting new studies and sites for review by the IRB. (See IRB Meeting Calendar).

3.7 PAYMENT FOR SERVICES (IRB MEMBERS)

IRB Members will either be consultants to the IIRB, Inc. and paid for consultation services or will be considered employees of IIRB, Inc. and IRB services will be paid as part of their salary. Liability coverage is provided for IRB Members.

4 IRB REVIEW

The IRB is empowered to grant approvals, require modifications to approvals, or deny approvals for research studies consistent with applicable regulations conducted under the oversight of IIRB, Inc. The IRB may require informed consent form and/or protocol modification, consultation, additional information and/or clarifications as part of the review process. The IRB will require progress reports and is authorized to approve, modify or deny continued approval. The IRB may suspend or terminate approval at any time if there are any changes to the research, risks or if any problems with the research are identified. The IIRB,

Inc. may observe, or have a third party observe, the consent process and/or the conduct of the research.

4.1 COOPERATIVE RESEARCH

IIRB, Inc. does not generally participate in cooperative research review as defined under 56.114 (for FDA research) and 45 CFR 46.114 (for federally funded research) as these requirements refer to the role of an institutional local IRB.

4.2 REVIEW OF RESEARCH CONDUCTED AT A SITE WITH A LOCAL IRB

When research is conducted in a hospital, outpatient surgical center, or ambulatory care center (such as Planned Parenthood), a Facility Waiver Form is required. The Facility Waiver Form documents that the facility accepts the review services of the IIRB, Inc. and if the facility has a local IRB, that the local IRB waives jurisdiction. The form serves as notification to the facility of the research. In addition, a copy of the facility's most recent License/JCAHO certificate (or equivalent) is required to be provided to the IIRB, Inc. for assessment of the adequacy of the facility.

The IRB at IIRB, Inc. serves only as a primary IRB for the review of research. If a research study is reviewed by another IRB for another site, the informed consent form that was approved for that previous site can be submitted to IIRB, Inc., however, the IRB of IIRB, Inc. will make changes to the informed consent form as deemed necessary and will complete a comprehensive review and approval of the research as required by the IIRB, Inc. HRPP Plan. If changes to the research informed consent form are required, the rationale will be documented.

4.3 CONSULTATIONS

The IIRB, Inc. offers human research determination and exemption determination as part of consultation services for clients.

4.3.1 DETERMINATION OF RESEARCH INVOLVING HUMAN SUBJECTS

All research involving human subjects conducted under the oversight of the IIRB, Inc. must follow this HRPP Plan. Determining whether an activity is research involving human subjects will be based on all applicable regulations, federal and state, under which research determinations must be made (e.g., 45 CFR 46 for DHHS regulations, 21CFR 56 for FDA regulations). The Human Subjects Research Determination Checklist serves as a tool for this assessment.

The responsibility for initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this determination based on the definitions of "human subject" and "research." Investigators can contact the IIRB, Inc. to request a confirmation that an activity does not constitute human subjects research. This is a service provided by IIRB, Inc. to Investigators and is not a requirement. The request may be made verbally, by phone contact, by email or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination including but not limited to a research protocol and product information.

The determination includes (1) determining that the activity is considered a clinical investigation or research as defined by FDA regulations (21 CFR 50.3(c)) and if so, whether it involves human research participants as defined by FDA regulations, (2) determining if the activity is research as defined by DHHS regulations (45 CFR 46.102(d)) and if so, whether it involves human research participants as defined by DHHS regulations. Human Research Participant (subject) as defined by DHHS regulations is defined in the HRPP Plan Glossary. If the activity meets either (1) or (2), it is considered "research involving human subjects." The criteria for making these determinations are listed in 45 CFR 46.102(f), 21 CFR 50.3(c) and 21 CFR 50.3(g).

A Qualified Screening Staff may provide verbal consultation regarding determination, but written confirmation can be made only by an IRB Member. The IRB Member will complete both the Human Subject Research Determination Form (FDA) and the Human Research Determination Form (Non-FDA) to determine whether the activity is human subject research and to determine whether FDA and/or DHHS regulations apply.

Formal submissions will be responded to in writing, and the determination will be communicated to the investigator (if applicable). A copy of the submitted materials and determination letter/email will be kept on file.

4.3.2 EXEMPTION

The IIRB, Inc provides exemption determination as a service to clients. The Investigator will submit a request for exemption, which will include a summary of the research, a description of the research procedures, plans for privacy, confidentiality, dissemination of findings, and expected date of completion.

A Qualified Screening Staff will review the Request for Exemption Determination Form and submitted documentation for completeness and provide them to an IRB Member for exemption determination. The IRB Member will use the guidelines listed in that form to determine whether the protocol meets the exemption criteria. The IRB Member will evaluate the submission to determine if the research plan abides by the ethical principles of the organization including that of the Belmont Report focusing on beneficence, respect for persons and justice.

A Letter of Exemption Determination will be provided to the Investigator and reported to the IRB at the next scheduled IRB meeting. The granting of an "Exempt" status to a research project does not preclude the need for additional review for compliance with HIPAA regulations, or adherence to the principles outlined in the Belmont Report.

4.4 HIPAA AUTHORIZATION AND WAIVER

The IRB can conduct HIPAA Waiver reviews. These reviews are generally limited to access database information. Research documentation that outlines the plan and provides necessary justification for approval is required. The files will be maintained consistent with the procedures listed in the IRB Records and Files section.

4.5 SUBMISSION REQUIREMENTS

In order for a research study to be reviewed by the IRB, a Research Protocol, Investigator's Brochure or Device Brochure or Product Information Package (as applicable), Form FDA 1572 (if applicable), complete Site Questionnaire(s) and relevant documentation, draft Informed Consent Form(s) (as applicable), Request for IRB review, qualifications of Investigators and other relevant study documentation is requested by the Friday prior to a Tuesday IRB Meeting. A member of the Administrative Staff will review the submission for completeness. If the submission is incomplete the Administrative Staff will contact the Investigator, CRO, or Sponsor as warranted to request documents or information missing from the submission.

4.6 FILE PREPARATION PROCESS

The following outlines procedures for preparing a file for review.

4.6.1 ADMINISTRATIVE STAFF (PROJECT LEADERS)

The Project Leader will initiate the research file set up and review the file to determine if all necessary components are provided and to initiate follow up as warranted to obtain complete documentation.

4.6.2 RESEARCH SCREENING

All initial submissions will be screened by a Qualified Screening Staff for determination of completeness and accuracy. The Qualified Screening Staff initiates the Research Evaluation Process and Form. Any findings or recommendations that the Qualified Screening Staff identifies will be documented on the Research Evaluation Form and provided to the IRB on the Board Evaluation portion of the Research Evaluation Form with the research study file.

A Qualified Screening Staff or designee will notify the investigator if the submission is incomplete, or if additional documentation or clarification is necessary. If the submission is incomplete the research study will not be placed on the agenda for review until the submission is considered complete. The Qualified Screening Staff may identify that additional consultation from an individual listed on our Consultation Roster is necessary and will initiate contact.

The Research Evaluation Form and any possible areas of concern will be provided to the attention of the Chair/Designee prior to the IRB meeting.

4.7 CRITERIA FOR IRB APPROVAL

In order to approve a research study the IRB or the expedited reviewer, when reviewing by expedited review procedures, must determine that all of the requirements in 21 CFR 56.111 45 CFR 46.111, or 40 CFR 26.111 are satisfied. The criteria include:

- Risks to subjects are minimized:
  - by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
  - whenever appropriate, by using procedures already being performed on the

subjects for diagnostic or treatment purposes.

- Risks to subjects are reasonable in relation to anticipated benefits, if any, and to 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 even if not participating in the research.
  - The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- selection of subjects is equitable
- informed consent is sought, documented and is thorough and consistent with Federal regulations
- where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of the subjects (i.e., ongoing sponsor compliance monitoring and safety monitoring including dose escalation studies)
- where appropriate, there are adequate provisions to protect the privacy of subjects and maintain confidentiality of data
- appropriate safeguards are included in the study to protect the rights and welfare of vulnerable subjects and additional safeguards for other research participants that may also be at risk (i.e., handicapped, economically disadvantaged, compromised health status, and employees)

4.7.1 RISK/BENEFIT ASSESSMENT

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

1. judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;
2. disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research - one of the major responsibilities of the IRB - involves a series of steps:

1. **identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive if not participating in research;
2. **determine whether the risks will be minimized** to the extent possible;
3. **identify the probable benefits** to be derived from the research;
4. **determine whether the risks are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained;
5. **ensure that potential subjects will be provided with an accurate and fair description** of the risks or discomforts and the anticipated benefits;

Risks to subjects are minimized:

1. by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
2. whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

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

1. 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 if not participating in the research.
2. The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

4.7.1.1 SCIENTIFIC MERIT

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question; and
- The knowledge expected to result from this research is sufficiently important to justify the risk.

In making this determination, the IRB may draw on its own knowledge and disciplinary expertise, or the IRB may draw on the knowledge and disciplinary expertise of an outside consultant or source.

4.7.2 SELECTION OF SUBJECTS IS EQUITABLE

The IRB determines by viewing the application, protocol and other research project materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not adequately provide for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who may benefit or be a benefit to the research. In making this determination, the IRB evaluates: the purposes of the research; the setting in which the research occurs; scientific and ethical justification for including vulnerable populations such as children, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit or be a benefit to the research; and the inclusion/exclusion criteria.

At the time of continuing review the IRB will determine if the PI has followed the subject selection criteria that he/she originally set forth at the time of the initial IRB review and approval.

The determination and evaluation of equitability includes all subject recruitment materials and processes. See Research Subject Recruitment section for more details.

4.7.3 INFORMED CONSENT

The IRB will ensure that 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 45 CFR 46.116, 21 CFR 50.20, 40 CFR 26.116. In addition, the IRB will ensure that informed consent will be appropriately documented in accordance with, and to the extent required by 45 CFR 46.117, 21 CFR 50.27, 40 CFR 26.117. See Attachment 10 for detailed policies and documentation of informed consent.

4.7.4 DATA SAFETY MONITORING

For all research that is more than minimal risk, the initial submission to the IRB should describe the procedures for data safety monitoring either by the inclusion of elements listed in the research protocol, establishment of a Data and Safety Monitoring Board (DSMB), or by other supporting documentation. If the elements for data safety monitoring are not adequately addressed in the research protocol or other supporting documentation, the Investigator will be notified that a separate safety-monitoring plan is required. Investigators may use the Data and Safety Monitoring Plan Form as a guidance tool for fulfilling this requirement.

When the IRB determines if data and safety monitoring is appropriate, the IRB will consider the following:

- Reporting mechanisms
- Frequency of the monitoring, such as points in time or after a specific number of participants are enrolled.
- Entity that will conduct monitoring, such as a data monitoring committee, medical monitor, investigator, or independent physician.
- Specific data to be monitored.
- Procedures for analysis and interpretation of data.
- Actions to be taken upon specific events or end points.
- Procedures for communication of unanticipated problems involving risk to subjects or others to the IRB and sites.

The IRB determines that, where appropriate, the research plan makes adequate provisions for monitoring data to ensure safety of subjects and integrity of the study. In general, it is desirable for a Data and Safety Monitoring Board to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. When DSMBs are utilized, the IRB may request a current statement from the DSMB at the time of continuing review.

4.7.5 PRIVACY AND CONFIDENTIALITY

The IRB will determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of "Personal Health Information (PHI)" and protection of study data. The IRB considers issues of privacy related to the protection given to respecting the individual, while confidentiality relates to the protection of "Personal Health

Information " and study data. The nature of the study will impact the need for privacy and confidentiality including the sensitivity of the information being gathered.

The Investigator will provide information regarding research subject privacy and confidentiality at the time of initial review and continuing review through the completion of the Site Questionnaire, submission of the Research Protocol, and/or other submitted applicable materials. The IRB will review all information received and determine whether or not the privacy and confidentiality of research subjects is sufficiently protected.

Reporting of breaches of privacy and confidentiality are reviewed during the study through the review of unanticipated problems involving risks to participants or others.

4.7.5.1 PRIVACY

The IRB will determine whether the research activities support respect for the research participant's rights of privacy. In order to make this determination, the IRB obtains information regarding how Investigators are accessing subjects, interviewing subjects and the adequacy and resources of the research facility.

In making the determination regarding the adequacy of privacy measures the IRB assesses that the Site Questionnaire/and or research protocol has addressed:

1. Settings in which an individual will be interacting with an investigator or site personnel include attention to maintaining privacy.
2. Personnel present for research activities are limited to appropriate individuals.
3. The research facility has adequate physical space and privacy mechanisms to support participant privacy.
4. If the research involves the collection of information about individuals other than the "target participants," protective measures are included (e.g., a subject provides information about a family member for a survey) that protect the privacy of these individuals.

4.7.5.2 CONFIDENTIALITY

The IRB will determine whether the research site and plan include mechanisms to maintain the confidentiality of "Personal Health Information" and protection of study data. In order to make that determination, the IRB obtains information regarding how Investigators are accessing subjects' information and the subject's expectations of confidentiality in the research situation. Investigators are required to have appropriate authorization to access the subjects or the subjects' information. The IRB does this through the evaluation of the methods used to obtain information about subjects, and individuals who may be recruited to participate in studies, the use of personally identifiable records, and the methods used to protect the confidentiality of research data.

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harm that would likely result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

4.7.6 VULNERABLE POPULATIONS

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards are put into place for vulnerable subjects, such as those without decision-making capacity. Enrollment of vulnerable populations is included in the Site Questionnaire, and the IRB may also require standard operating procedures be submitted for review with the study submission to identify additional safeguards for vulnerable populations.

The IRB may require that someone other than the primary care provider conduct the informed consent session and that additional measures for evaluating capacity to consent are in place. The IRB carefully evaluates each protocol to determine if vulnerable subjects are included in the study population and what measures have been taken to protect them.

The IRB is required to consider the scientific and ethical reasons for including vulnerable populations in research. The IRB will review specific elements of the research plan when reviewing research involving vulnerable subjects. These specific elements may include strategic issues such as inclusion and exclusion criteria for selecting and recruiting participants, informed consent and willingness to volunteer, coercion and undue influence and confidentiality of data.

The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects. Investigators are not permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.

The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB. The IRB may also require that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, see Attachment 12.

4.8 INVESTIGATIONAL DRUGS AND DEVICES

4.8.1 IND REQUIREMENTS

The IRB will assess if an IND is required for the conduct of the research study. The Investigator may be required to provide documentation regarding the IND status of the research. If it is determined that an IND is NOT required, the IRB will document the criteria upon which this determination is based by means of the Research Evaluation Form. If an IND is required, documented assurance from the sponsor including known risk information and that the manufacture and formulation of investigational or unlicensed test articles conforms to federal regulations is necessary. Documentation of the IND could be a:

1. Industry sponsored protocol with IND.
2. Letter from FDA.
3. Letter from industry sponsor.
4. Other document and/or communication verifying the IND.

The Investigator Brochure cannot be used to validate an IND.

4.8.2 REVIEW OF DEVICE STUDIES

The IRB will assess a research study and determine if the research study includes an FDA regulated device and if a risk determination is required. The Investigator may be required to provide documentation regarding the IDE status of the research. Documentation of the IDE could be a:

1. Industry sponsored protocol with IDE.
2. Letter from FDA.
3. Letter from industry sponsor.
4. Other document and/or communication verifying the IDE.

The Investigator Brochure cannot be used to validate an IDE number.

If the research includes an FDA regulated device and the FDA has already made the SR or NSR determination for a device study, the agency's determination is final and the IRB does not need to make a risk determination.

If the device does not have an IDE, the IRB will confirm that either (1) the device meets the abbreviated IDE requirements in 21 CFR 812.2(b); or (2) the device meets one of the IDE exemptions in 21 CFR 812.2(c)(1)-(7). Part of making a determination of whether a device fulfills the criteria for abbreviated IDE requirements is confirming that the device is not a significant risk device.

As part of making a determination of whether a device fulfills the criteria for the abbreviated IDE requirements, the IRB will review the device study and determine if the device represents significant or non-significant risk based on information from regulatory requirements and guidelines, including close consultation with experts from the Food and Drug Administration, the FDA Information Sheet Guidance for IRBs, Investigators, and Sponsors; Significant Risk and Nonsignificant Risk Medical Device Studies - January 2006 and from information from the Sponsor/Applicant. A risk determination is always required for devices that meet the abbreviated IDE requirements and the IRB will document this determination. The IRB will provide the Sponsor/Investigator and/or CRO with the IRB Findings.

If the IRB determines that the study has an IDE or is exempt, no risk determination needs to be made by the IRB.

If a study that has been submitted as meeting the abbreviated IDE requirements does not meet the abbreviated requirements and/or the exempt from IDE requirements, the IRB may not approve the study until an IDE is obtained.

4.8.3 APPROVAL OF INDS PENDING FDA REVIEW

At the time of study submission it is necessary to identify if an IND number has been assigned or if it is pending FDA 30 day review. The following considerations will be given related to the review of research study during this 30 day review period.

- The IRB can review a research study during this 30 day review period.
- The IRB **may** approve the research study and can permit that subjects be screened for the study based on IRB determination.
- Dosing is not permitted until the IRB has been notified in writing that the 30 day review period has elapsed without a clinical hold by the FDA, and/or any substantial changes to the protocol.
- The following outlines reasons that it is possible that the IRB may approve the research study but **will not** permit screening of subjects during this 30 day review period:
  - A wash-out from routine treatment medications is required following the screening visit (i.e., diabetic medication),
  - The screening procedures require more than minimal risk procedures.
- It is possible that the IRB will not approve a research study during this period if there is reason that the IRB is concerned that the FDA may not ultimately grant the IND or there are research design concerns.

4.8.4 PI AS SPONSOR

When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Site Questionnaire asks the PI if he/she will act as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the appropriate section of the Investigator's Guidebook and will comply with the regulatory responsibilities of a sponsor.

4.9 RESEARCH SUBJECT RECRUITMENT AND PAYMENT

4.9.1 RESEARCH SUBJECT RECRUITMENT/ADVERTISEMENT

Research subject recruitment includes mechanisms for an equitable selection of subjects and includes that both the burdens and benefits of the research are equitable and selection of subjects is justified by the science. Recruitment of subjects must recognize cultural and local customs. The IRB recognizes the informed consent process can include elements of recruitment and therefore attention to the consent process is necessary to assure that it is implemented in a way that is equitable to all subjects.

4.9.2 RESEARCH PARTICIPANT RECRUITMENT MATERIALS

All forms of subject recruitment (advertisement) for a research study must be approved by the IRB prior to implementation. Subject recruitment includes any information that is provided

for the purpose of recruiting subjects, such as; newspaper advertisements, script for video or radio advertisement, brochures, internet Web Page, flyers and posters. The advertisement must not be misleading and must be consistent with the research protocol and informed consent form.

The review of all forms of advertisement will ensure that the advertisements:

- Material is accurate
- Not coercive or unduly optimistic
- Does not promise a favorable outcome or "free treatment"
- Does not imply the study medication or device is safe or superior to other treatments thereby creating undue influence on the subject to participate
- Make subjects aware that the research involves an investigational product
- Do not include exculpatory language
- Do not emphasize the payment or the amount to be paid, by such means as larger or bold type
- Are limited to the information prospective participants needed to determine their eligibility and interest, such as:
    - The name and address of the investigator or research facility
    - The purpose of the research or the condition under study
    - In summary form, the criteria that would be used to determine eligibility for the study
    - A brief list of participation benefits, if any
    - The time or other commitment required of the participants
    - The location of the research and the person or office to contact for further information
- For FDA-regulated research:
    - Do not use terms, such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational
    - Do not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it had been approved for marketing

For video script(s) and audio scripts, a final version must be submitted to the Independent Investigational Review Board, Inc. for review prior to use. No undue vocal emphasis on payment to research subjects or potential benefits is permitted. For print advertisement(s), the relative size of the font referencing payment or potential benefits cannot be any more prominent than other information contained within the advertisement(s). A final version, if revisions or reformatting is required, must be submitted to the Independent Investigational Review Board, Inc. for review prior to use. The information contained in the final copy of the recruitment material (advertisement) will be reviewed and the mode of its communication will be evaluated.

No changes to or use of additional advertisements is permitted without prior approval. Advertisements can be approved by Expedited Review with reporting at the next meeting.

The evaluation of recruitment materials and advertisements is documented in the written approval/disapproval letter provided to the Investigator.

4.9.3 ADVERTORIALS

The IRB may review and approve advertorials for use in research studies. The IIRB, Inc. considers an advertorial as an advertisement that is written and presented in the style of an editorial or journalistic report. An advertorial will be considered as subject recruitment materials based on the content of the submission and determination that the information provided is for the purpose of recruiting research subjects. Although the advertorial is for the purpose of creating interest in research participation, no study specific recruitment language is permitted. If it is determined that the advertorial is intended for subject recruitment purposes, it must be approved by the IRB through routine recruitment processes. Additional scrutiny to verify accuracy is required due to the potential for confusion in distinguishing between an advertising article and standard journalistic articles, particularly because they appear in the same typeface as other contents of the newspaper or magazine.

Additional scrutiny includes supporting documentation of facts and claims from a reliable source and that disease-specific information is objective and is not misleading. The advertorial must be consistent with the requirements of the HRPP Plan and FDA Guidance documents for recruitment materials. Information about how and where the advertorial will be utilized and how it will appear in final form is also required for consideration of approval of an advertorial. Confirmation that the advertorial will be placed with the title "Advertisement" is also necessary.

The submission of an advertorial should provide the following information for review:

- The advertorial text and artwork, in the font (size and style) and layout intended for publication
- Reference citations for all factual information in the advertorial, ***whether or not*** these citations will appear in the advertorial
- Information about the context in which the advertorial will be utilized (e.g., type of publication, description of readership)
- Identification if the advertorial will be placed in conjunction with a separate study specific advertisement

4.9.4 PAYMENT TO RESEARCH SUBJECTS

The IIRB, Inc. will consider "Payment to Subjects" separately from the benefits of the study. The IIRB, Inc. will review the amount of the payment and the method of disbursement to assure that neither present evidence of coercion or undue influence. Payment will be pro-rated if the subject does not complete the study. An undue amount of the total stipend will not be withheld if the subject does not complete the research study. Payment and method of disbursement must be documented in the informed consent form.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study may be given, providing that such incentive is not coercive. The IRB will determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. The IRB will use 15% of the total stipend as a baseline guide for completion payment and incentives to continue participation. Based on the nature of the study and total duration, the IRB may determine that a

completion bonus or incentives greater than 15% may be acceptable. Payments must be made on at least a yearly basis for studies with durations longer than 12 months.

The IIRB, Inc. considers "wash-out" to refer to the period when a research participant is being taken off of their regular medications to determine if they may qualify for a research study. The IRB considers that when a washout is done in anticipation of or in preparation for the research, it is part of the research (FDA Information sheets). The research participant is entitled to payment for that portion of the washout that is completed on a prorated basis.

The IIRB, Inc. considers "continued participation" as any portion of the study following dosing, which requires that the participant conduct study required procedures. Examples include; at home dosing, blood sugar monitoring, diary completion, and telephone contacts. The research participant is entitled to payment for those day/procedures completed on a prorated basis.

Although the IIRB, Inc. does not generally consider observing restrictions between research visits as compensable, consideration can be given to compensation for observing restrictions provided that the compensation is not contingent upon completing the subsequent research visit. If the compensation is contingent upon completing the visit (no mechanism for prorating the payment is provided) this payment in reality is considered payment for attending the study visit and will be added to the payment for that visit.

4.9.5 INDICATION OF PAYMENT IN ADVERTISEMENTS

Advertisements may indicate that subjects will be paid for their participation in the research study. However, special attention, in review of the advertisement will be given to verifying that there is no undue emphasis on payment, (i.e. use of $$ signs as graphics, bold type or larger font). In addition, no use of any exculpatory language is permitted.

4.9.6 RECEPTIONIST SCRIPTS

Receptionist Scripts, where a prospective study subject calls to find out about a study that has been advertised do not require specific IRB review and approval. The first contact a prospective study subject makes is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB will assure the procedures followed adequately protect the rights and welfare of the prospective subjects through the Site Evaluation Plan. In some cases personal and sensitive information is gathered about the individual which may be used as inclusion/exclusion criteria for participation in a research study. The IRB should have assurance that the information will be appropriately handled.

4.10 EMERGENCY USE REVIEW

The IRB does not review studies in which investigational drugs/devices or biological products are used as emergency intervention (in a life-threatening situation) for which no standard acceptable treatment is available.

4.11 RESEARCH UNDER EPA

The organization will review research under the Environmental Protection Agency (EPA). In addition to the basic procedures and protections contained in the Common Rule, the Final

Rule also requires researchers who propose to conduct new research covered by the rule to submit protocols and other materials for science and ethics review by both EPA and a newly created Human Studies Review Board (HSRB). The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App.2 § 9. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research. The HSRB shall comment on the scientific and ethical aspects of research proposals and reports of completed research with human subjects submitted by EPA for its review and on request, advise EPA on ways to strengthen its programs for protection of human subjects of research 40 C.F.R. 26.1603(b). The HSRB review of proposed new research would occur following its review and "approval by the IRB" and after EPA developed its review.

All research reviewed under EPA regulations will follow the review procedures listed in the IRB Review Process section of the HRPP Plan. Documentation of approved research will be distributed to all applicable parties (i.e., Sponsor, CRO, or Investigator.) It is the responsibility of the Principal Investigator to ensure that required subsequent reviews by EPA, by the EPA Human Studies Review Board (HSRB,) and if the research is to be conducted in California, by the California Department of Pesticide Regulation (CDPR) have been completed before initiation of the study. This responsibility has been communicated in the Investigator's Guidebook. The IIRB, Inc., requires that the Investigator or Sponsor report IIRB, Inc. approval to EPA and, if applicable, to CDPR, and confirm to IIRB, Inc., that all required regulatory reviews have been conducted. Recommendations by EPA, HSRB, or CDPR should be incorporated into revised proposals and submitted to IIRB, Inc., for review and approval before enrollment of any research participants in the study. Initiation of a study conducted for submission to EPA before obtaining all required regulatory reviews or before final approval of the protocol, consent form(s), and supporting materials by the reviewing IRB is a violation of EPA regulations and will be treated as non-compliance. Such events will be reviewed according to the Reports of Non-Compliance section of this document.

5 IRB REVIEW PROCESS

5.1 EXPEDITED REVIEW

The Chair of the IRB will appoint qualified IRB Members to conduct expedited review. The appointment of Expedited Reviewers will be documented in their Training and Education File.

The categories of research eligible for consideration are limited to those categories listed in section 56.110, published on January 27, 1981 [46 FR 8980]. Expedited action regarding research conducted under DHHS/OHRP Guidelines will be taken by an Expedited Reviewer limited to those categories authorized by 45 CFR 46.110, 21 CFR 56.110, and 40 CFR 26.110 contained in the list published on November 9, 1998 in 63 FR60364.

The Expedited Reviewer may give expedited approval to (1) initial or continuing review of research activities that meet all applicability criteria and fall into one or more categories described in Categories of Research That May be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure, or (2) minor changes in previously approved research during the period which approval is granted.

The expedited reviewer will evaluate whether research undergoing initial review and continuing review using the expedited procedure (1) meets all applicability criteria, and (2) represents one or more approvable categories of research. The expedited reviewer will evaluate whether modifications to previously approved research undergoing review represents a "minor" modification.

Federal regulations permit the use of the expedited review procedure to review "minor" modifications to a previously approved protocol. A minor change will not involve procedures that increase risk more than minimally or add procedures that would make the protocol ineligible for initial review using the expedited procedure, such as procedures that involve exposure to ionizing radiation.

The determination that changes to previously approved research are "minor" is generally understood as; no more than minimum (as defined in FDA and DHHS regulations), the risk/benefit relationship is not altered in a way that makes it less favorable, does not compromise the rights of subjects or is immediately necessary.

In addition, a minor change is one which, in the judgment of the Expedited Reviewer, makes no substantial alteration in:

1. the level of risks to subjects
2. the research design or methodology (adding procedures that are not eligible for expedited review would not be considered a minor change)
3. the number of subjects enrolled in the research (no greater than 15% of the total requested)
4. the qualifications of the research team
5. the facilities available to support safe conduct of the research
6. any other factor which would warrant review of the proposed changes by the convened IRB
7. significant payment to subjects (no more than 15% increase) however, in a minimal risk study this percentage can be reconsidered based on the total stipend.

Examples of minor changes include:

1. Changes in location or Sub-Investigators (other than change to Principal Investigator)
2. Revisions to Informed Consent Forms that do not increase risks, do not exceed a 15% increase of subjects enrolled, or exceed a 15% increase in payment to subjects.
3. Revised Protocol or Amendment that does not increase risks to subjects and does not exceed a 15% increase of subjects enrolled.
4. Advertisements and Recruitment material

The Expedited Reviewer may request additional input from other members of the IRB in order to make the decision as to whether or not expedited action can be taken. No provision however, is established that any member of the IRB other than the Expedited Reviewers are authorized to grant expedited approval to any submission, action or request.

All expedited review submissions will be screened by a Qualified Screening Staff for determination of completeness and accuracy and to recommend if the submission meets

criteria for expedited review. A Qualified Screening Staff or designee will notify the investigator if the submission is incomplete or if additional documentation or clarification is identified as necessary.

The reviewer will receive the same materials that the convened IRB would have received and will be conducted following the same procedures as if the research study or modification was reviewed by the convened IRB.

The Expedited Reviewer may approve the expedited action or can determine that the submission requires full IRB review for any reason, including but not limited to; the requested action is related to the identification of an unanticipated problem involving risks to participants or others in research, the requested action may be related to serious or continuing non-compliance or may warrant suspension or termination or be in response to a recent suspension or termination, the expedited request affects a special population (e.g., pediatric), or there is a potential COI. A research activity may be disapproved or tabled only after review in accordance with the non-expedited review procedures. The Expedited Reviewer will document review of the item on a transaction checklist for each submitted item and the documentation will be filed in the study file.

If a research project is suspended the Investigator will be notified and will be given an opportunity to provide additional information. This action must be presented for IRB review to finalize status of the research and determine if other actions are warranted.

The Expedited Reviewer will document his/her review in the appropriate Approvable Material Checklist, approval letter, and Expedited Action Listing. The Expedited Action Listing outlining these findings will be reported to the IRB at the next regularly scheduled IRB meeting.

5.2 REVIEW AT CONVENED IRB MEETING

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all research at convened meetings in which a quorum of the members is present.

5.2.1 IRB MEETING PROCEDURES

The Chair and Vice Chair may be present at the same meeting, however only one will be responsible for serving as the Chair of the meeting and the other will serve as a voting member. The IRB Chair or Vice Chair designated to serve as the Chair for a given meeting, will determine if a quorum is in place before calling the meeting to order. The Chair or Vice Chair will inquire and determine if there is a conflict of interest with any of the IRB members attending the current meeting. If there is a conflict of interest, the Chair or Vice Chair will remind the IRB member(s) to recuse themselves from the discussion and vote by leaving the room when the study is presented. The IRB will review and discuss the IRB Minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the Minutes will be accepted as presented and considered final. If it is determined that revisions/ corrections are necessary, the Minutes will be amended and presented at the following IRB meeting.

The IRB will review a summary of the actions taken by expedited review.

The IRB reviews submissions for initial and continuing review, unanticipated problems involving risks to participants or others in research, serious or continuing non-compliance, and suspensions and terminations as well as requests for modifications that do not meet criteria for expedited review. The Chair or Vice Chair presents an overview of the research and leads the IRB through completion of the regulatory criteria for approval after considering the findings on the research evaluation portion of the Research Evaluation Form and by reviewing the board evaluation portion of the Research Evaluation Form (see Research Evaluation Process and Plan-Attachment 4 for more details). At any time during the review process a member of the IRB may request consultation from an expert who is not a member of the IRB.

The IRB may require the presence of the Investigator or invite an Investigator to attend a meeting in person or via teleconference to answer questions regarding the proposed clinical investigation. An "invitation" is in no way a "requirement" and if the Principal Investigator is not available to attend, this will not adversely influence the IRB in its decision making process. The determination to invite an Investigator for discussion at a meeting is at the discretion of the IRB and is made based on the nature of the clarification as determined by the IRB. A Principal Investigator may request the opportunity to address the IRB, either at the time that the research is reviewed or in response to an action taken by the IRB. If the Principal Investigator is not available to attend, a physician Sub Investigator, familiar with the research protocol may respond to the IRB invitation. The only individual that is permitted to attend the meeting, is the individual specifically invited or requested to attend (or a predetermined IIRB, Inc. approved designee) and the request is not an invitation to the Study Team. Discussion related to the IRB's final decision is made without the Principal Investigator present at the meeting and the IRB will inform the Principal Investigator of the IRB's decision following the processes outlined in the HRPP Plan. In addition, the Investigator is not allowed to vote.

Documentation of specific determinations required under the regulations and protocol-specific findings that justify the determinations will be documented on the Board Evaluation portion of the Research Evaluation Form. The Research Evaluation Form including the Board Evaluation portion of the form will be used as guidelines in the review process. These forms are intended to minimize the opportunity for IRB error and improve documentation of compliance. These forms will either be kept filed with the protocol file or electronically stored in the IRB database system.

The Chair will lead the IRB discussion through the following criteria in order to determine if the study meets the criteria listed 45 CFR 46.111, 21 CFR 56 §111, or 40 CFR 26.111 for approval. See Criteria for IRB Approval section for more details.

It is the responsibility of an IRB Liaison or designee who serves as a liaison between the IRB and Administrative Staff to record the findings of the session.

5.2.2 QUORUM/VOTING PROCEDURES

The IIRB, Inc. considers majority to be more than 50% of the IRB members (not including

alternates). The total number of IRB members ÷ 2 = x, whereas x cannot be < 5 and must be a whole number. If x = a half number, x will be rounded to the next whole number. See table below.

Numbers of IRB Members	5	6	7	8	9	10	11	12	13	14	15
Majority Equals	5	5	5	5	5	6	6	7	7	8	8

IRB members with conflicting interest do not count towards quorum. A majority vote of members present is required for any official IRB action. The quorum is calculated based on the total number of voting Primary IRB Members listed on the Membership Roster and recorded in the Minutes as either Present, Also Present or Absent. Alternates are designated as an alternate for specific members. Alternates count as voting Members only when they are fulfilling the role of the Member who is Absent. In this situation the Absent Member is designated in the minutes as "Absent", and the Alternate Member is designated in the minutes as "Present." There may be situations that the Member and their Alternate are both present at the meeting. In this situation, the Member is considered "Present" and the Alternate is considered "Also Present" (meaning that they are present, however, they do not have a vote and do not count towards a quorum). A physician and a non-scientific member must be part of the majority. IRB members with conflicting interest do not count towards quorum. The Chair and Vice Chair may be present at the same meeting, however only one will be responsible for serving as the Chair of the meeting and the other will serve as a voting member.

If quorum is lost during a meeting the IRB cannot take votes until it is restored. If a member temporarily leaves the room discussion will be suspended.

The physical presence of IRB Members is required for members to be considered "Present". The Chair, at his/her discretion, may accept written comments (fax/e-mail) and telephone comments from IRB Members unable to attend meetings for informational purposes but these written comments are not considered information needed for assessing criteria for approval and does not allow the IRB Member to vote by proxy.

5.2.3 MEETING RECORDS/MINUTES

The IRB will maintain minutes of each meeting and will review and vote on the Approval of the minutes of the previous meeting before consideration of any other business. Prior to approval, members may request changes in the minutes; however, all changes require IRB approval.

Minutes of IRB meetings must contain sufficient detail to show:

a. Actions taken by the IRB.
b. Separate deliberations for each action.
c. Votes for each protocol as numbers for, against, or abstaining.
d. Attendance at the meeting including names of members present, absent members, consultants present, Investigators present, and guests present
Note: The initial attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members

who enter or leave the meeting. The vote on each action will reflect those members present for the vote.

e. When an alternate member replaces a primary member.
f. The basis for requiring changes in research.
g. The basis for disapproving research.
h. A written summary of the discussion of controverted issues and their resolution.
i. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document, if any.
j. For initial and continuing review, the approval period.
k. The names of IRB members who leave the meeting because of a conflicting interest along with the fact that a conflicting interest is the reason for the absence.
l. Determinations required by the regulations and protocol-specific findings justifying those determinations for:
    a. Waiver or alteration of the consent process.
    b. Research involving pregnant women, fetuses, and neonates.
    c. Research involving prisoners.
    d. Research involving children.
m. The rationale for significant risk/non-significant risk device determinations.

Minutes shall include any comments members may specifically request to appear in the minutes. The minutes will also address all discussions listed on the Agenda and any other business brought before the IRB.

A copy of the approved IRB minutes outlining the actions of the IRB including suspension and termination, unanticipated problems involving risks to participants or others, and serious and/or continuing non-compliance will be provided to the IO of the IIRB, Inc. for review and acknowledgement.

5.3 REVIEW OF MULTI-SITE RESEARCH

A multi-site research study is defined as a research study that is being conducted at more than one research site/Principal Investigator under the oversight of the IIRB, Inc. whereas the IIRB, Inc. acts as a designated central IRB. The IIRB, Inc. will be contracted by a Sponsor or CRO to act as a central IRB.

The review of multi-site research can either be conducted whereas each site is considered a modification to ongoing research, or can be individually reviewed as a new research study for each site. At the time that the IIRB, Inc. is contracted to serve as the central IRB, the method for review of additional sites (i.e., modification vs. individually reviewed) will be determined. All additional sites will be reviewed under the method determined at the time that the study is submitted to the IIRB, Inc. unless the IO determines that due to documented extraneous circumstances a change in review method is required.

5.3.1 REVIEW AS INDIVIDUAL RESEARCH STUDY AND SITE

If a study is currently being conducted at another site under the oversight of the IIRB, Inc.

and is therefore considered a multi-site study and the new site is not considered a modification to ongoing research, the research study and research site will both be reviewed and evaluated according to the procedures listed under the IRB Review Process. Therefore, each site submitted will be reviewed as a new submission of research and each site will be given an individual approval period as indicated in the Duration of Approval section.

5.3.2 REVIEW AS MODIFICATION TO ONGOING RESEARCH

When the addition of a new investigator and research site to a previously approved protocol is considered a modification to an approved protocol, the research protocol and supporting study documents are first reviewed and approved by the convened IRB prior to the review of additional sites. This initial review does not require investigator/site information.

During the initial review of the research study, the IRB will evaluate the following documentation to determine if the research study meets the elements of the Criteria for Approval (not including specific site evaluations elements): The research protocol and supporting study documentation can include

- Research Protocol (required)
- Investigator's Brochure or Device Brochure or Product Information Package (as applicable)
- Draft Sample Informed Consent Form (including additional consents such as Photography Form, Assent Form, Pharmacogenetic Form, etc.) (as applicable)
- Template advertisements or recruitment material (as applicable)
- Research participant study materials (as applicable)
- Other relevant documents pertaining to the research study

If the IRB determines that the research study meets the Criteria for Approval (not including specific site evaluations elements) the study will be granted an Approval and an approval period will be determined according to the procedures listed in the Duration of Approval section. This will be considered the date in which continuing review of the research study is required and will not exceed one year.

The actions of the IRB will be documented in the IRB Meeting Minutes. The Sponsor/CRO will be notified of the actions made by the IRB. The Sponsor/CRO will also receive a reviewed template Informed Consent Form. This template Informed Consent Form is stamped "Approved" and is not for use in recruiting or consenting subjects. The Sponsor/CRO will be advised that a Continuing Review Report is required prior to the approval interval expiration.

5.3.2.1 ADDITIONAL SITE APPROVAL

Individual research investigators/sites can be added as study modifications to an approved research study. The IRB considers a change in Principal Investigator to be more than a minor change in previously approved research and therefore does not meet criteria for expedited review procedures. The site must submit all necessary site specific information and the site must be approved by the IRB prior to the commencement of any research activities related to the approved study protocol at their site.

The additional site submission documentation includes the following for IRB review:

- Completed Site Questionnaire
- Form FDA 1572 (if applicable)
- Qualifications of Investigator(s)
- Request for IRB review (Submission Letter)
- Advertisements or Recruitment material
- Any other relevant documentation pertaining to the site

The IRB will evaluate the submitted information according to the Site Evaluation Process (see Attachment 3). If the site submission supports the elements for Criteria for Approval, the IRB will grant the Investigator/site an Approval and an individual approval interval will be determined based on the procedures listed in the Duration of Approval section but cannot exceed the expiration date of the research study. The Investigator will be notified of the actions made by the IRB and the actions will be documented in the IRB Meeting Minutes. In addition, the investigator will be provided with an approved Informed Consent Form that is stamped "Approved" for use in consenting subjects, and notification that the study can commence at the approved location. The investigator/site will be advised that a Progress Report Form is required prior to the expiration date of the research study.

5.4 ROLE OF CONSULTANTS IN THE REVIEW PROCESS

The need for consultation with an individual that is not a member of the IRB may be identified through the screening process prior to presentation of the research at the IRB meeting or by the IRB at the time of presentation of the research. The reasons for consultation may include but are not limited to; assistance in the review of issues or protocols, which require scientific or scholarly expertise beyond, or in addition to that which is available on the IRB representation or in the review of research involving a vulnerable population.

A Qualified Screening Staff, with consultation from others as required, will evaluate each protocol and compare the expertise required to review the protocols to the IRB members expected to be present at the meeting in terms of (1) scientific expertise, (2) knowledge about or experience in working with participants, (3) vulnerability to coercion or undue influence, when the research involves such individuals, (4) other requirements related to appropriate expertise. The Qualified Screening Staff will consult with the Chair or Vice Chair to consider deferring the review to another meeting or obtain consultation if appropriate expertise is not available at the time.

The consultation may be recommended by a Qualified Screening Staff or IRB member from a list of available consultants that indicates specific competence in special areas. The Consultant will be provided with all relevant materials necessary to conduct the review. The consultant's role and responsibilities include reviewing materials such as the Research Protocol, Investigator's Brochure/Safety documentation, Informed Consent Form(s), and other relevant documentation in which their specific expertise is warranted. The consultant's findings will be presented to the full IRB for consideration either in person, in writing or as reported by the Chair or Vice Chair. If in attendance, these individuals will provide

consultation but may not vote. Opinions provided by Consultants will be documented in the study file.

A Consultant's qualifications will be kept on file or will be obtained prior to the distribution of information pertaining to the expertise of the consultant. Qualifications include a copy of the consultant's curriculum vitae and license if applicable, along with a signed Member/Consultant Confidentiality Agreement and Internal Conflict of Interest and Disclosure Form (see Conflict of Interest Plan (Internal and External)-Attachment 2 for more information).

If the IRB determines at a meeting the use of a consultant is necessary in order for review of a study, the study will be given a "Tabled" status until such consultation is obtained.

5.5 IRB ACTION

The IRB shall render Approval, Contingent Approval, Disapproval, Table, or Administratively Close as an action. The vote will be recorded in the Minutes of the meeting for all actions.

The Expedited Reviewers are authorized to sign any other approval documents submitted by the investigator; however, these approvals cannot supersede, modify, or alter stated conditions on the IRB Approval Letter.

The Investigator shall have the opportunity to respond to any decision made by the IRB in person or in writing for appeal purposes. To respond in person, the Investigator must notify the Chair or Vice Chair to schedule a visit. All responses shall first be reviewed by a Qualified Screening Staff and Chair or Vice Chair. If the response requests or requires modification to a previously approved protocol the response will first be reviewed by the Chair or Vice Chair to determine if the action can be reviewed using the expedited review procedures and if not eligible or expedited review the response will be placed on the next agenda for review by the convened IRB.

5.5.1 APPROVAL

When the IRB grants approval, an Approval Letter shall be signed by an authorized signatory official and provided to the Investigator. The Approval Letter includes the date of review, documents that were reviewed, and the approval status of the research study. The duration of approval with expiration date will be included. In addition, the Approval Letter will include a notice to the Investigator that prompt reporting to the IIRB, Inc. of any serious adverse reactions, significant deviations from the protocol or problems in the research is mandatory. If appropriate, information will be provided to the Institution where the research will be conducted.

5.5.2 APPROVED AS SUBMITTED

The research as submitted is acceptable and no changes are required.

5.5.3 APPROVED WITH CHANGES

The research is approved based on the changes in the consent form directed by the IRB. Handwritten changes to the consent form are incorporated by the Administrative Staff, and

reviewed by a Qualified Screening Staff for accuracy prior to final signature.

5.5.4 CONTINGENT APPROVAL

The IRB can render a contingent approval of a submission if (1) the investigator or sponsor request to review changes made by the IRB prior to approval; (2) minor documentation or changes are required that the IRB stipulates implementation through simple concurrence by the Investigator; (3) minor substantiating documentation is requested. The pending documentation and changes made by the sponsor or Investigator cannot affect the Criteria for Approval. These revisions and additional documentation will be reviewed by expedited review procedures.

When the IRB grants a study a "Contingent Approval," the Investigator will have an opportunity to respond to the action made by the IRB. The written response must be received within the approval period. If no written response is received within the approval period, the IRB will consider the study for closure.

5.5.5 TABLING OF RESEARCH

The IRB may determine to render a "Tabled" action of a submission based on pending additional information or clarification of the research study.

When the IRB considers a submission "Tabled," a Tabled Letter will be promptly written and signed by an authorized signatory official and provided to the Investigator. The Tabled Letter will include the reasons for Tabling the submission, actions that the Investigator can take to resubmit the submission for review (i.e., modifications to the research protocol, modifications to the informed consent form, or providing additional information/documentation), and basis for these modifications. Copies of the Tabled Letter will be provided to appropriate institutions (including Sponsor, Contract Research Organization, etc.).

Submissions in response to Tabled studies must be reviewed by the IRB.

5.5.6 DISAPPROVAL OF RESEARCH

When the IRB disapproves the clinical investigation, a Disapproval of Research Letter shall be promptly written and signed by an authorized signatory official and provided to the Investigator. This letter will state the reasons for disapproval. Copies of the Disapproval of Research Letter will be forwarded to appropriate institutions (including Sponsor, Contract Research Organization, etc.) or to the Food & Drug Administration and DHHS as warranted.

The Disapproval of Research Letter will include that an Investigator has 10 business days to appeal the determination. Submissions in response to a Disapproval of Research Letter must be reviewed by the IRB.

5.5.7 ADMINISTRATIVE CLOSURE

When the IRB considers a study "Tabled," the Investigator will have an opportunity to respond to the action made by the IRB. The written response must be received by the IRB within 90 days of the date of the action made by the IRB. If no written response is received

within the 90 day period, the IRB will issue an Administrative Closure Letter. If a response is submitted after the 90 day period, the submission will be reviewed according to initial review procedures.

5.6 DURATION OF APPROVAL

The criteria for the approval period will be determined based on the following but not limited to;

- the nature of the study
- the degree of risk involved
- the vulnerability of the study population
- the projected length of the study

The approval period is established at the time of initial approval of the research study and may not exceed one year. When additional sites are reviewed as modifications to previously approved research, the approval period of the additional site is established when the site is reviewed and approved by the convened IRB and cannot exceed the expiration date previously determined for the research study and cannot exceed one year. The IRB will determine the duration of the approval period by discussion at the time of the initial approval and continuing review. The IRB may determine the duration of approval is less than one year based on the criteria listed below:

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

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The overall qualifications of the PI and other members of the research team.
4. The specific experience of the Responsible Investigator and other members of the research team in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events more likely.
7. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case exceeds 1 year. The number of subjects

studied or enrolled determines the approval period only when that number of subjects studied or enrolled is less than 1 year.

When the IRB approves a protocol the expiration date is calculated on the basis of the date of the convened meeting at which the research is approved. For Contingent Approvals, the start date of the approval period begins on the day that the research was reviewed by the IRB and contingent approval was granted.

The approval period will remain as long as the research remains active for long-term participant follow-up, even when permanently closed to enrollment and participants have completed research-related interventions, or as long as activities include analysis of identifiable data.

The approval period is clearly noted on all IRB Initial Approval Letters and Continuing Review Approval Letters sent to the Investigator and must be strictly adhered to. Review of a change to a protocol ordinarily does not alter the date by which continuing review must occur (i.e., approval of modifications to previously approved research does not extend the approval period). To calculate the expiration date, the day that the study was approved by the IRB or by an Expedited Reviewer will serve as the start day of the approval period. The approval period in months (i.e., 12 months, 6 months, 3 months) will be added to the original start date. The expiration date will be the day prior to the end of the approval period and will expire at midnight. For example, a study approved on May 3, 2008 for a 12 month period would expire on May 2, 2009 at midnight and a study approved on May 3, 2008 for 6 months would expire on November 2, 2008.

5.7 CONTINUING REVIEW

It is the Investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date listed on the initial Approval Letter or subsequent continuing reviewer letters. To assist investigators, the Administrative Staff will send out reminder notices approximately one month and two weeks prior to the expiration date. The Investigator may apply for continuing review by completing a Progress Report Form, or may close the study by completing a Study Closeout Form. The investigator is not obligated to use these forms, but must supply a written response summarizing the results of the research and addressing the criteria in the applicable form.

Should the Investigator for an approved study fail to supply the appropriate Progress Report Form or Study Closeout Report for clinical investigations prior to the expiration of the study's approval, the Chair or Vice Chair shall so advise the IRB and study approval will expire and the Investigator will be notified.

The information provided by the Investigator for review by the IRB will include at least the following, but is not limited to:

- Enrollment activity, study status, a summary of events such as adverse events that would alter the risk/benefit assessment, a summary of unanticipated problems involving risks to participants or others, a summary of drop outs, a summary of changes in the research, risks, benefits and information about the study.

- Current Informed Consent Form signed by a subject including any additional consents (i.e. Addendums, DNA ICF) and any translations for verification that the correct and most current form is being utilized.
- Current copy of the Principal Investigator's medical license.
- Any changes to the research study that were not previously submitted.

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

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

1. 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.
2. Protocols conducted by Principal Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
3. Protocols randomly selected for internal audit.
4. Whenever else the IRB deems verification from outside sources is relevant.

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

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

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

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

All continuing review submissions will be screened by a Qualified Screening Staff for determination of completeness and accuracy. The Qualified Screening Staff will review the initial Research Evaluation Form or other initial review documentation and make updates as warranted. Any findings or recommendations that the Qualified Screening Staff identifies will be documented on the Research Evaluation Form and provided to the IRB for review with the research study file. If the electronic version of the Research Evaluation Form is not available, the Qualified Screening Staff will document findings for IRB review. A Qualified Screening Staff will notify the Investigator, Site, or Sponsor as appropriate if the submission

is incomplete or if additional documentation or clarification is identified as necessary. If the submission is incomplete the research study will not be placed on the agenda for review until the submission is considered complete. In addition, a Qualified Screening Staff will review the continuing review submission prior to review by the IRB to ensure that the study has been screened, the submission is complete, and the study is ready for IRB review.

For continuing review of a protocol by a convened IRB the IRB members (including alternates when filling in the role of a primary IRB member) will review the following information as applicable:

- The sponsor protocol.
- The following information, if not in the sponsor protocol:
    - A description of procedures already being performed for diagnostic or treatment purposes.
    - When some or all of the participants are likely to be vulnerable, a description of additional safeguards included in the protocol to protect their rights and welfare.
- The current consent document.
- Any newly proposed consent document.
- Progress Report Form/Continuing Review Report

For continuing review of research by the convened IRB, at least one IRB member will review in depth the complete protocol including any protocol modifications previously approved by the IRB.

The IRB will review the file to determine if all required elements of 40 CFR 26/45 CFR 46/21 CFR 56 §111 continue to be met. In addition the IRB will determine if there are any significant new findings which may relate to subjects willingness to continue their participation in the study, and if the best interests of individual participants are served by continued involvement in the research.

The IRB may determine that; (1) the research study continues to meet the criteria for approval, (2) additional information is required, (3) modifications to the study protocol or informed consent form are required, or (4) may determine the research study be closed. IRB findings will be documented on the Board Evaluation portion of the Research Evaluation Form (or supplemental forms if the electronic version of the Research Evaluation and Board Evaluation Form is not available), in the IRB meeting minutes, and communicated to the Investigator, CRO, Sponsor, and any applicable regulatory agency if necessary. The IRB will determine the duration for ongoing approval based on the criteria outlined for initial approval duration.

Should the clinical Investigator for an approved study fail to supply the appropriate continuing review information for clinical investigations prior to the expiration of the study's approval, the Chair or Vice Chair shall so advise the IRB and study approval will expire and the Investigator will be notified. All research activities must stop, unless the IRB finds an over-riding safety concern or ethical issue such as the best interests of individual participants are served by continuing the study. The IRB may request that the Investigator report if any

subjects are currently enrolled, in order to determine if safety concerns or ethical concerns may arise if research activities are stopped. Copies of this notice will be forwarded to any appropriate institutions, Sponsors, CRO or Regulatory Authorities.

The continuation of research after expiration of IRB approval is a violation of the regulations [21 CFR 56.103(a)]. If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities should stop. No new subjects may be enrolled in the study. However, if the investigator is actively pursuing renewal with the IRB and the IRB believes that an over-riding safety concern or ethical issue is involved, the IRB may permit the study to continue for the brief time required to complete the review process.

5.7.1 CONTINUING REVIEW MULTI-SITE RESEARCH

5.7.1.1 CONTINUING REVIEW AS INDIVIDUAL RESEARCH STUDY AND SITE

If a study is currently being conducted at another site under the oversight of the IIRB, Inc. and the new site is not considered a modification to ongoing research and was reviewed as an individual research study, the research study and the research site will both be reviewed and evaluated for continuing review according to the procedures listed under the Continuing Review section.

5.7.1.2 CONTINUING REVIEW AS MODIFICATION TO ONGOING RESEARCH

At the end of the approval period of the research study determined at the time of initial review of a protocol, the study Sponsor/CRO must submit a Continuing Review Report. To assist the Sponsor/CRO the Administrative Staff will send out reminder notices approximately two months and one month prior to the expiration date of the study to notify them that a Continuing Review Report is due. The Continuing Review Report provides a cumulative summary of the following information compiled from all sites:

- Number of participants accrued study-wide.
- A study-wide summary since the last IRB review of:
  - Adverse events.
  - Unanticipated problems involving risks to participants or others.
  - Participant withdrawals.
  - The reasons for withdrawals.
  - Complaints about the research.
  - Amendments or modifications.
- Any relevant recent literature.
- Any interim findings.
- Any relevant multi-center trial reports.
- The sponsor's current risk-potential benefit assessment based on study results.
- Verification of the most recent protocol, Investigator's Brochure or Product Information.
- Any changes to the research study that were not previously submitted.

In addition, all sites approved as a modification to ongoing research during the approval

period of the research study must submit a Multi-Site Progress Report Form in order for the IRB to verify the data provided. To assist Investigators, the Administrative Staff will send out reminder notices to investigators approximately one month and two weeks prior to the expiration date.

The information provided by the site for review by the IRB will include at least the following, but is not limited to:

- Current Informed Consent Form signed by a subject including any additional consents (i.e. Addendums, DNA ICF) and any translations for verification that the correct and most current form is being utilized.
- Current copy of the Principal Investigator's medical license.
- Multi-Site Progress Report Form.
- Any site specific changes to the research that were not previously submitted.

The Continuing Review Report and each Multi-Site Progress Report Form will be screened by a Qualified Screening Staff for determination of completeness, accuracy, and to compile an internal summary of findings for IRB review. The Qualified Screening Staff will review the initial Research Evaluation Form or other initial review documentation and make updates as warranted. Any findings or recommendations that the Qualified Screening Staff identifies will be documented on the Research Evaluation Form (or supplemental forms if the electronic version of the Research Evaluation and Board Evaluation Form is not available) and provided to the IRB for review with the research study file. The submission will be placed on the agenda for review by the IRB. In addition, a Qualified Screening Staff will review the continuing review submission prior to IRB review to ensure that the study has been screened, the submission is complete, and the study is ready for IRB review.

The completed continuing review submission is defined by the following:

- Completed Continuing Review Report by Sponsor/CRO
- Completed Multi-Site Progress Report Forms for sites approved as modifications during the approval period
- Internal summary of findings from Qualified Screening Staff

For continuing review of a protocol by a convened IRB, the IRB members (including alternates when filling in the role of a primary IRB member) will receive and review the documents as listed in the Document Distribution Plan (Attachment 13). In addition, at least one IRB member will review in depth the complete protocol including any protocol modifications previously approved by the IRB.

The IRB will review the submission to determine if all required elements of 40 CFR 26/45 CFR 46/21 CFR 56 §111 continue to be met. In addition the IRB will determine if there are any significant new findings which may relate to subjects' willingness to continue their participation in the study, and if the best interests of individual participants are served by continued involvement in the research.

The IRB may determine that; (1) the research study continues to meet the criteria for approval, and issue approval to continue to conduct the research study for all or some sites

(2) additional information is required, (3) modifications to the study protocol or informed consent form is required, or (4) may determine that the research study be closed. The IRB will determine the duration for ongoing approval based on the criteria outlined under the Duration of Approval section. IRB findings will be documented on the Board Evaluation portion of the Research Evaluation Form, in the IRB meeting minutes, and communicated to the CRO, Sponsor, and applicable regulatory agency as appropriate.

If the IIRB, Inc. is unsuccessful in the collection of the information, the Chair or Vice Chair will notify the IRB of the status and the study's approval (including each site approved as modifications to conduct the study) will be considered for withdrawal. In addition, any site that does not provide necessary documentation will not be considered for re-approval at the time of continuing review of the research.

When the approval of a research study or the approval of a site to conduct an approved research study is withdrawn, all research activities must stop, unless the IRB finds an over-riding safety concern or ethical issue such that the best interests of individual participants are served by continuing the study. The IRB may request that the Investigator report if any subjects are currently enrolled, in order to determine if safety concerns or ethical concerns may arise if research activities are stopped. Copies of this notice will be forwarded to the investigator, and appropriate institutions, Sponsors, CRO or Regulatory Authorities.

5.7.2 CONTINUING REVIEW THROUGH EXPEDITED REVIEW PROCEDURES

Continuing reviews may be conducted using expedited procedures (see expedited review procedures) if the research study meets the following criteria (63 FR 60364-60367, November 9, 1998):

- The initial review of the study was conducted using expedited review procedures and the research study continues to meet the criteria for expedited review.

- Category 8: Continuing review of research previously approved by the convened IRB as follows:
    - 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
    - Where no subjects have been enrolled and no additional risks have been identified; or
    - Where the remaining research activities are limited to data analysis.

- Category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) (of 63 FR 60364-60367, November 9, 1998) 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.

In addition, the following applicability criteria must be determined:

- The research presents no more than minimal risk to subjects. (Not applicable for category (8)(b))
- The identification of the subjects or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their 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. (Not applicable for category (8)(b))
- The research is not classified.

Studies that meet category 9 criteria listed above may be eligible for continuing review using the expedited review procedure. The three applicability criteria apply to all categories except as noted. Reviewers will document whether research meets category (8)(a), (8)(b), or (8)(c) on the Expedited Review Checklist (Initial and Continuing Review).

5.8 MODIFICATIONS OF ONGOING RESEARCH

Modifications to ongoing research may be made through a Protocol Amendment, a Sponsor/Site Letter, Updated Investigator's Brochure, Potential Unanticipated Problem or Serious and/or Continuing Non-Compliance Form, or a report of Non-Compliance. Modification such as unanticipated problems involving risk to subjects or others or serious or continuing non-compliance must be reported to the IIRB, Inc. within (10) business days of receiving notice of the event.

The submission will be evaluated to determine if the submission indicates a change in research and requires approval either under expedited review procedures or review by the IRB (i.e., amendment, recruitment material, and revised informed consent form). If the submission is a change in research and meets criteria for a minor change in research, the submission will be reviewed under expedited review procedures. Reported modification to ongoing approved research studies will be evaluated to determine if the modification is an unanticipated problem involving risks to participants or others, or evidence of serious or continuing non-compliance. If the modification is either an unanticipated problem involving risks to participants or others or evidence of serious or continuing non-compliance, the modification will be handled under the procedures listed for each type of event. Minor modifications that are not unanticipated problems involving risks to participants or others, serious or continuing non-compliance, and do not require approval are considered new information and may be reviewed under the procedures listed in the Administrative Review section.

Implementation of modifications to research is not permitted prior to IRB approval unless necessary to eliminate immediate hazards. Particular attention is paid to modifications that change the risks to the subjects and verification of the need for modification to a consent form. The IRB will determine whether significant new findings that may relate to subjects' willingness to continue taking part in the research need to be provided to the subjects. If enrollment is completed, a Consent Addendum may be utilized.

5.9 UNANTICIPATED PROBLEMS INVOLVING RISKS TO PARTICIPANTS OR OTHERS

An unanticipated problem involving risks to participants or others is defined as (1) unexpected and (2) indicates that participants or others are at increased risk of harm. A Qualified Screening Staff will evaluate submissions that have the potential to be an unanticipated problem in research. Problems that are scientific in nature will be screened by a scientific Qualified Screening Staff. Unanticipated problems that are non-scientific in nature can be screened by either a scientific or non-scientific Qualified Screening Staff

If the Qualified Screening Staff is unable to make a determination, the report will be presented to the IRB Chair or Vice Chair for determination. If the Chair or Vice Chair is unable to make a determination, the event will be reviewed by the IRB. If it is determined that the report is not an unanticipated problem involving risks to participants or others, no further action is taken under this policy but the report will be evaluated under the procedures listed in the Reports of Non-Compliance section and if applicable under Administrative Review procedures. If a Qualified Screening Staff, Chair, Vice Chair, or convened IRB determine that the report is an unanticipated problem involving risks to participants or others, the problem will be placed on the agenda of the next IRB meeting for discussion.

All unanticipated problems involving risks to subjects or others must be submitted to the IIRB, Inc. regardless of whether they occur during the study, after the study completion, or after subjects withdraw or complete the study. Sponsors who identify such findings during routine monitoring are responsible for reporting these problems to the IIRB, Inc.

The following are potential unanticipated problems that may require reporting to IIRB, Inc.:

a. Adverse events which in the opinion of the Principal Investigator are both unexpected and related.
b. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., Investigators, research assistants, students, the public, etc.) to potential risk
c. Information that indicates a change to the risks or potential benefits of the research. For example:
    a. An interim analysis or safety monitoring report indicate that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
    b. A paper is published from another study that shows the risks or potential benefits of the research may be different than initially presented to the IRB.
d. A breach of confidentiality or breach of subject's rights.
e. Incarceration of a participant in a protocol not approved to enroll prisoners.
f. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
g. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
h. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.

i. Event that requires prompt reporting to the sponsor.
j. Sponsor imposed suspension for risk.
k. Any other problem that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.
l. Any trends that may indicate a pattern of problems or unanticipated risks (patterns of protocol deviations or adverse events that singularly may not be significant, but together pose a possible trend).
m. Studies placed on FDA or Administrative Hold.

Investigators are to submit a Potential Unanticipated Problem or Serious or Continuing Non-Compliance Form or sufficient documentation containing the information to IIRB, Inc. for the above problems.

A Qualified Screening Staff, Chair, Vice Chair, or convened IRB may determine the submitted problem includes a finding of "non-compliance" with research requirements. If the determination is made that the event is due to serious or continuing non-compliance, the procedures under Reports of Non-Compliance will be followed.

For the review of an unanticipated problem involving risks to participants or others by the convened IRB the Qualified Screening Staff will provide all IRB members with a copy of:

- Potential Unanticipated Problem or Serious and/or Continuing Non-Compliance Form
- Supporting information
- Results of any investigation
- If the problem is relevant to a specific protocol:
    - The protocol
    - The consent document
- If the problem is relevant to a specific investigator or site:
    - The site file.

The IRB will consider the following actions:

- Suspension of the research.
- Termination of the research.
- Notification of participants when information about non-compliance may affect their willingness to continue participation.
- Modification of the protocol.
- Modification of the information disclosed during the consent process.
- Provide additional information to past subjects.
- Require current subjects to re-consent to participation.
- Modification of the continuing review schedule.
- Monitoring of the research.
- Monitoring of the consent.
- Referral to other organizational entities.

After review by the convened IRB the reporting procedures listed under the Notification to the FDA/EPA/DHHS/OHRP section are followed as applicable.

Documentation of findings by the IRB will be included in the unanticipated problem involving risks to participants or others letter provided to the Investigator and documented in the IRB Meeting Minutes. The investigator may be asked to attend the IRB meeting in person or via teleconference to answer any questions or clarify issues for the IRB.

5.10 IDENTIFICATION OF NEW INFORMATION

New information can be submitted in the form of an Investigational New Drug Safety Report, Pregnancy Notification, Protocol Deviation, Revised Form 1572, Revised Investigator Brochure or Product Information, Serious Adverse Event, or other sponsor/site notifications. All new information that does not require approval and does not appear to be the result of an unanticipated problem involving risks to participants or others or serious or continuing non-compliance will be reviewed under the procedures listed in the Administrative Review section.

5.10.1 ADMINISTRATIVE REVIEW

Submitted items that do not require approval (i.e. IRB review or Expedited Review) and do not meet the criteria for serious or continuing non-compliance or unanticipated problem involving risks to subjects or others will be reviewed under administrative review. An administrative review will be conducted by Qualified Screening Staff.

The administrative staff will provide the submission documentation and study file to a qualified individual. The qualified individual will review the submission and determine if the event meets criteria for serious or continuing non-compliance or an unanticipated problem involving risks to subjects or others and therefore requires IRB review. The qualified individual will also evaluate if the submission meets criteria for an approvable material.

If the submission does not require approval, the qualified individual will review the submission for accuracy, appropriateness, and consistency with the protocol. The Principal Investigator and Sponsor/CRO as appropriate will be notified of this administrative review action.

If the item requires approval it will be reviewed to assess if the item is potentially eligible to be reviewed under expedited review procedures. If the item is potentially eligible, the submission will be provided to an Expedited Reviewer to determine if it meets criteria for expedited review and if so, reviewed under expedited review procedures. If the submission does not meet criteria for expedited review, it will be reviewed by the convened IRB.

5.11 REPORTS OF NON-COMPLIANCE

Reports of non-compliance with regulatory or ethical principles may be reported by an Investigator, CRO, Sponsor, regulatory agency, current subject or potential subject. Investigators and research staff have to report non-compliance to the IRB if it is the result of potential serious and/or continuing non-compliance. The report should be provided in writing to the attention of the IRB, however, if the individual reporting the allegation requests to remain anonymous, a verbal statement will be accepted.

5.11.1 ALLEGATIONS OF NON-COMPLIANCE

A Qualified Screening Staff will investigate the allegation to evaluate if the allegation is based on fact and appears to be true in nature. In evaluating the allegation, the Qualified Screening Staff will review the allegation of non-compliance, the study protocol, current Informed Consent Form, Investigator's Brochure or Product Information, the study file including history of reports of non-compliance as necessary, and any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

The Qualified Screening Staff will review the allegation and make a determination as to the truthfulness of the allegation. They may request additional information or an audit of the research in question. If the Qualified Screening Staff determines the allegation has no basis in fact, no further action is taken. If allegations are determined with a basis in fact the allegation is handled as findings of non-compliance. If the Qualified Screening Staff cannot make a determination of the allegation, the allegation will be referred to the Chair or Vice Chair for determination. If the Chair or Vice Chair cannot make a determination of the allegation, it will be referred to the convened IRB for review.

5.11.2 FINDINGS OF NON-COMPLIANCE

A Qualified Screening Staff will evaluate if non-compliance is (1) serious non-compliance, and/or (2) continuing non-compliance. The Qualified Screening Staff will also evaluate whether there is information that is unexpected and increases the risks to subjects or others.

If there is information that is both unexpected and increases the risks to subjects or others the allegation will be reviewed according to the procedures listed in the Unanticipated Problem section.

If, in the judgment of the Qualified Screening Staff , the reported finding of non-compliance is not serious, not continuing, and the proposed corrective action plan is adequate, no further action is required and the event is reviewed under the procedures listed in the Administrative Review section. Reports of non-compliance that are submitted and determined to be neither serious nor continuing will be filed in the study file, and will be reviewed when an additional report of non-compliance is made and at the time of continuing review to determine if continuation of non-compliance is evident. If the event is potentially serious or continuing, non-compliance is managed as serious or continuing non-compliance and will be placed on the agenda for review by the convened IRB.

The IRB members will receive the report of non-compliance, protocol, currently approved informed consent form as necessary, and any other documents that may be relevant to the report of non-compliance. The allegation will be assessed by the IRB and the IRB will evaluate if the event is serious and/or continuing. In addition, the IRB will determine if a corrective action plan will be determined. Corrective actions may include the following:

1. Request a correction action plan from the investigator.
2. Verification that participant selection is appropriate and observation of the actual informed consent process.
3. Conduct a site visit.
4. An increase in data and safety monitoring of the research activity.

5. Request a directed audit of areas of concern.
6. Request a status report after each participant receives notification.
7. Modify the continuing review period.
8. Request additional Investigator and staff education.
9. Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation in the study.
10. Require modification of the protocol.
11. Require modification of the information disclosed during the consent process.
12. Require current participants to re-consent to participation in the study.
13. Suspend or terminate the study (See Suspension and Termination of IRB Approval Section).

When there is a determination that indicates serious or continuing non-compliance, the reporting procedures listed in the Notification to the FDA/EPA/DHHS/OHRP section are followed as applicable. Serious and continuing noncompliance is defined in the HRPP Plan Glossary. See Site Evaluation Plan (Attachment 3) and Continuous Quality Improvement Monitoring Program Plan (Attachment 8) for more details.

5.12 RESEARCH PROTOCOL DEVIATIONS

Any protocol deviations that meet the criteria for an unanticipated problem must be evaluated and actions taken as defined in the Unanticipated Problem section. Any protocol deviations that meet the criteria for non-compliance must be evaluated and actions taken as defined in the Reports of Non-Compliance section and may be reviewed under the procedures listed for Administrative Review.

5.13 SUBJECTS CONTACTING IIRB, INC.

Research Subjects may contact the IIRB Inc. for any reason including to report problems, express concerns, ask questions, request information, or to provide input. Subjects can voice these issues by contacting the IIRB, Inc. office by telephone, mailing a letter, fax, or by emailing information. The contact information in which subjects can use to relay this information is included in the informed consent form, and is located in the Research Participant section of the IIRB, Inc. website.

Any subject contact that meets the criteria for unanticipated problem must be reported as defined in the Unanticipated Problem section. Any subject contact that is received by the IIRB, Inc. will also be assessed as a possible unanticipated problem and if confirmed as an unanticipated problem it will be reviewed under the procedures listed for Unanticipated Problems. Any subject contact that indicates an allegation or finding of non-compliance will be managed by the procedures listed in the Reports of Non-Compliance Section.

If a subject contact does not meet criteria for unanticipated problem involving risks to participants or others or serious or continuing non-compliance, it will be handled by a qualified screening staff and reported to the IO. The IO will evaluate the subject contact and determine if the IOAG and IRB should be advised of the complaint. If warranted the site will be notified and follow up will be instituted.

5.14 SUSPENSION OR TERMINATION OF IRB APPROVAL

The IRB will implement suspension or termination of IRB approval of research in accordance with 21 CFR 56.113, 45 CFR 46.113, or 40 CFR 26.113. Suspension of IRB approval is a directive of the IRB, Chair or Vice Chair either to temporarily or permanently stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the IRB to permanently stop all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The IRB has the authority to suspend or terminate approval of research not being conducted in accordance with IIRB, Inc., regulatory requirements or that has been associated with unanticipated problems, or serious harm to subjects.

The IRB Chair or Vice Chair may suspend research to ensure protection of the rights and welfare of research participants. The complete research file including applicable documentation such as the research protocol, current consent form, Investigator's Brochure, history of unanticipated problems, and history of non-compliance will be reviewed and an assessment of the event will be conducted. The Chair or Vice Chair may decide temporary suspension of the study is warranted until the event is reviewed at the next IRB meeting. Suspension directives made by the Chair or Vice Chair must be reported to a meeting of the IRB. Research may only be terminated by the full convened IRB. If the next scheduled meeting is not within 10 days of the issuance of the suspension, a special meeting shall be convened.

When a study's approval is suspended or terminated, the IRB, Chair, or Vice-Chair ordering the suspension or termination may determine that withdrawal of enrolled subjects is necessary in order to protect their rights and welfare. The IRB, Chair, or Vice-Chair will evaluate the methods in which subjects should be withdrawn. This may include transferring participants to another Investigator, making arrangements for care or follow-up outside the research, allowing continuation of some research activities under the supervision of an independent monitor, or requiring or permitting follow-up of participants for safety reasons. In addition, the IRB will determine if notification of current or former subjects is warranted, and may require all adverse events or outcomes of the study be reported to the IRB. The IRB will report these requirements to the Investigator.

The Principal Investigator, Research Sponsor/Contract Research Organization will be given the opportunity to provide clarification and information to the IRB for consideration and final determination.

When there is a suspension or termination of IRB approval the reporting procedures listed in the Notification to the FDA/EPA/DHHS/OHRP section are followed as applicable.

5.15 ADMINISTRATIVE HOLD

An Investigator or Sponsor may request an administrative hold of a research protocol when the Investigator or Sponsor wishes to temporarily or permanently stop some or all approved research activities. An administrative hold may be initiated by an Investigator or Sponsor may

be in response to a request by the IRB to modify the way the research is conducted. Administrative holds are not suspensions or terminations. The time period for approval is not effected by an Administrative Hold, and the study is still due for continuing review within the time period identified at the time of initial approval.

5.16 NOTIFICATION TO THE FDA/ EPA/DHHS/OHRP

The IIRB, Inc. will notify the investigator, appropriate institutional officials, the FDA, EPA and DHHS/OHRP, Sponsor and/or Contract Research Organization (CRO), as applicable, of any suspensions or terminations of previously approved research due to unanticipated problems involving risks to human subjects or others, and any serious or continuing noncompliance.

It is the responsibility of the Sponsor/CRO to report unanticipated problems and serious or continuing non-compliance to applicable regulatory agencies. If the IIRB, Inc. has not received notification that the unanticipated problems involving risks to human subjects or others or serious or continuing noncompliance has been reported as required, the IIRB, Inc. will follow the reporting procedures as indicated in this section.

The Chair, Vice Chair, or designee is responsible for preparing these notification reports or letters and include the following information:

a. Name of the institution conducting the research
b. Title of the research project
c. Name of the Principal Investigator
d. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
e. Actions the organization or IRB is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.) and the reasons for the organization's or IRB's action.
f. Plans, if any, for follow-up of the continued investigation

The report will be forwarded to the applicable regulatory agency(s):

a. FDA, when the research is FDA-regulated or results are intended to be submitted to the FDA.
b. OHRP, when research is covered by DHHS regulations or results are intended to be submitted to the DHHS.
c. EPA, when the research is covered by the EPA regulations or results are intended to be submitted to the EPA.
d. Other federal agencies when the research is overseen by those agencies, and requires separate reporting.

The IRB may determine that additional reporting may be warranted as applicable to:

a. other sites involved in the research,
b. Sponsor or Contract Research Organization,
c. supervisor of the Investigator

The IO ensures that all steps of this policy are completed within a timely manner (15 business days) between the recognition of a reportable event and fulfilling the reporting requirements. For more serious actions, the IO may expedite reporting.

6 IRB RECORDS AND FILES

The Chair and IO shall be responsible for maintaining IRB records, minutes, and files regarding IRB activities in accordance with the HRPP Plan and in accordance with the guidelines established by the Code of Federal Regulations covering such records.

IRB records may include as applicable, but are not limited to:

- Research protocols
- Investigators' brochures/Product Information
- Recruitment materials/Advertisements
- Scientific evaluations (if any) that accompany the study
- Approved consent documents, including DHHS-approved sample consent document and protocol
- HIPAA Authorization documents if separate from the informed sample consent documents
- Records of continuing review activities including Progress Report Form, and Study Closeout Report submitted by Investigators
- Any proposed modification to ongoing research
- Reports of Unanticipated Problems Involving Risks to Participants or Others Documentation of protocol deviation
- Documentation of non-compliance with applicable regulations
- Statements of significant new findings provided to subjects
- Consultation reports
- IRB membership roster(s)
- IRB meeting minutes
- Copies of all correspondence between the IIRB, Inc. and the Investigator
- Reports of injuries to participants.
- For exemption determinations, the category allowing the exemption.
- For initial and continuing review of research by the expedited review procedure:
    a. The specific permissible category.
    b. Description of action taken by the reviewer.
    c. Any findings required under the regulations.
- For each protocol's initial and continuing review, the frequency for the next continuing review.

IRB records must also document any determinations required by regulations and protocol-specific findings supporting those determinations, including:

- Waiver or alteration of the consent process.
- Research involving pregnant women, fetuses, and neonates.
- Research involving prisoners.
- Research involving children.

All records, minutes and files regarding IRB activities shall be accessible to IRB members upon request and shall be available with notification to appropriate officials for procedural reviews conducted by the FDA, the EPA and the DHHS.

6.1 PROTOCOL FILES

The Administrative Staff shall create a study file for each clinical investigation reviewed. The research file will contain all submitted materials and IRB response to the submission and Research Evaluation materials. The Administrative Staff shall be responsible for the maintenance of these files.

6.2 RECORD RETENTION

IRB records and files as described in the section titled "IRB Records and Files" must be stored securely at the IIRB, Inc. office or contracted off-site facility and must be retained for at least 3 years after study completion. The IIRB, Inc. considers study completion as either the date in which a Study Closeout Report was reviewed by the IIRB, Inc. and officially closed, the date the study approval was withdrawn due to the expiration of the study approval period, or the date in which a termination of the study was issued by the IRB. For multi-site studies, the completion date is the date that the study was closed at a particular site. After that time, records will be shredded or otherwise destroyed by a professional document destruction company, and a certificate of destruction will be provided. IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at the facility for at least 3 years after study completion.

All records must be accessible for inspection and copying by authorized representatives of the FDA, EPA, DHHS, sponsors, and other authorized entities at reasonable times and in a reasonable manner. Records are maintained in file cabinets and/or locked storage rooms at the IIRB, Inc. office and are available only to IRB members and IRB office staff. In addition, the IIRB, Inc. office is only accessible to authorized individuals.

7 RESPONSIBILITY OF INVESTIGATOR

All Investigators conducting research under the oversight of IIRB, Inc. are expected to fulfill all ethical and regulatory requirements according to the state/country in which the research study is being conducted. Principal Investigators are ultimately responsible for the conduct of research. Principal Investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

Investigators who conduct research involving human subjects must be knowledgeable of Good Clinical Practices (GCP) and FDA regulations particularly 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators" or 21 CFR 812, Subpart E, "Responsibilities of Investigators" for device studies and conduct research that is in accordance with the ethical principles in the Belmont Report. This information is documented in the Site Questionnaire.

The Investigator will be advised of these responsibilities when notified of the approval of the research study and will be directed to the Investigator's Guidebook for reference.

7.1 INVESTIGATORS CONTACTING THE IIRB, INC.

Investigators who have concerns or suggestions regarding the IIRB, Inc. Human Research Protection Program should contact the IO or designee regarding the issue, when appropriate. The IO or designee will research the issue, and when necessary, include the parties involved to form a response to the Investigator or make necessary procedural or policy modifications, as warranted. In addition, the Chair of the IRB and qualified screening staff will be available to address Investigators' questions, concerns and suggestions.

8 RELATIONSHIP WITH SPONSORS

The IIRB, Inc. does not conduct research and does not accept contracts from Sponsors to conduct research. The IIRB, Inc. provides IRB services to Sponsors. The Sponsor may require a contract to be executed prior to initiation of IRB services. The President of the IIRB, Inc. or the CEO of the IRB has signatory authority for these Sponsor contracts. The President or CEO will review Sponsor contracts for the following criteria:

1) A statement that the IIRB, Inc. will provide IRB services in accordance to applicable regulations and the IIRB, Inc. HRPP Plan.
2) A statement that the Sponsor will monitor the research and will report any unanticipated problems or findings that may affect the safety or participants or their willingness to continue participation in the study, influence the conduct of the study, or alter the IRB's approval to continue the study.

9 RELATIONSHIP TO ORGANIZATIONAL WORK INSTRUCTIONS

Work Instructions (WI) of the IIRB, Inc. will be established to provide procedural information related to how the Organization implements the HRPP Plan and actions of the IRB. The Organizational WIs are derived from the HRPP Plan. If at any time a discrepancy between the Organizational WI and the HRPP Plan is identified, action will be taken in accordance with the HRPP Plan. Action will be taken to rectify discrepancies as warranted. The HRPP Plan supersedes WI. In addition, FDA/EPA/DHHS and ICH/GCP Guidelines supersede both the HRPP Plan and the Organizational WI.