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 — 11/3/2010 Date of Approval

Kim Lerner, Chief Executive Officer — 11/3/2010 Date of Approval

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 (2l 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 at least every 5 years or more frequently at the request of the IO.

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 PHYSICIAN REFERRALS

Payment to Physicians can be permitted under certain circumstances for the identification of patients that may be appropriate candidates for participation in a research study being conducted by an outside research center that is not part of that physician's practice. The organization will review processes related to payments to physicians for referring patients to a research study. Payment to physicians must be made as reimbursement per time spent conducting related procedures and not per patient referred/enrolled in a research study. In addition, payment to the referring physician must not be contingent on the enrollment of the patient. Lastly, all recruitment material must be reviewed and approved prior to use. If a script will be used, the script should identify that participation in a clinical research study may not benefit them and if their condition may worsen (as applicable). The organization will consider such things as the protection of privacy and disclosure of potential for conflict of interest in assessment of the adequacy of the process for patient referrals for research participation.

4.9.7 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.

The determination if a change is "minor" will be at the discretion of the Expedited Reviewer. In general, a minor change is one which, in the judgment of the Expedited Reviewer, makes no substantial alteration in following:

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 approximately 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 approximately 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

If research was originally approved under expedited review procedures, than modifications to the research may be reviewed under expedited review procedures as long as the modification does not alter the research in such a way that it no longer meets the criteria for expedited review.

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 prior meetings that are ready for IRB review 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 a subsequent 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 meetings available for review before consideration of any other business. Minutes from previous meetings must be reviewed within 30 days of the meeting. 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. However, if a research study met the criteria for expedited review and was approved under expedited review procedures, than the review of individual research investigator/sites can be reviewed under 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 (30 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.

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

ORGANIZATIONAL CHART PLAN

HRPP PLAN ATTACHMENT 1

PURPOSE

The Organizational Chart provides an overview of the IIRB, Inc. reporting structure. The Organizational Chart identifies the relationships between the Board of Directors, IOAG, IRB, Managers, Administrative Staff, and Financial and Human Resource Personnel. See the Organizational Chart for more information.

SCOPE

The Organizational Chart is a component of the HRPP Plan and includes all areas of IIRB, Inc. responsibility and supervision. It generally identifies position by job title.

RESPONSIBILITY

The Organizational Chart Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG.

See attached Organizational Chart.

CONFLICT OF INTEREST PLAN (INTERNAL AND EXTERNAL)

HRPP PLAN ATTACHMENT 2

PURPOSE

IIRB, Inc. is committed to preserving the public trust in the integrity and quality of research conducted under its oversight by minimizing actual or perceived conflict of interest in the conduct of research.

The Conflict of Interest Plan includes the process to identify, manage, report and maintain information regarding potential and identified conflicts of interest. The COI Plan will delineate mechanisms for these processes.

SCOPE

The Conflict of Interest Plan (COI Plan) includes potential and identified conflicts reported by individuals within the IIRB, Inc. organization, IRB Members, IRB Consultants, and investigators and key research staff involved in research that is under the oversight of the IIRB, Inc.

These procedures apply to both financial and non-financial conflicts of interest and are guided by Code of Federal Regulations (Title 42 of the Code of Federal Regulations (CFR) Part 50 Subpart F) that promotes objectivity in research to ensure conflict of interests do not adversely affect the protection of participants or the credibility of IIRB, Inc.'s HRPP Plan. The Plan includes review and management mechanisms of internal and external COI. An internal COI is one in which occurs internally at IIRB, Inc. including Board of Directors, IRB Members, IO, Manager, Administrative Staff and any other relevant individuals within the organization and any of their immediate family members as defined in the HRPP Plan Glossary. An external COI is one in which occurs at the site of the investigation including investigators, key research staff and their immediate family members.

The COI Plan is reliant on the guidelines addressed in the AAMC Task Force on Financial Conflicts of Interest in Clinical Research report entitled "Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research."

RESPONSIBILITY

The Conflict of Interest Plan (Internal and External) is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

DEFINITIONS

Significant Financial Interest. Significant Financial Interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g. consulting fees or honoraria); equity interests (stocks, stock options or other ownership interests); and intellectual property rights (patents, copyrights and royalties from such rights).

The following potential conflict of interest criteria applies to all members of the Board of Directors, Institutional Official Advisory Group (IOAG), Investigational Review Board (IRB), Mangers, Administrative Staff, and Financial and Human Resource Personnel and any of their immediate family members.

1. Potentially serving as a member of any research team (i.e. investigators, key research staff, etc.) related to the review of studies by the IIRB, Inc.
2. Currently have or potentially having any ownership interest, stock options, or other equity interest with any organization related to the review of studies by the IIRB, Inc. greater than 5% of total equity.
3. Received or will potentially receive payments from any organization related to the review of studies by the IIRB, Inc. that exceeds $10,000 when aggregated for immediate family members in one year.
4. Currently have or have the potential to have a financial interest in any research reviewed by the IIRB, Inc. that values exceeds $10,000 when aggregated for immediate family members in one year.
5. Currently have or have the potential to have any proprietary interest in any research reviewed by the IIRB, Inc., such as a patent, trademark, copyright, or licensing agreement.
6. Currently have or have the potential to have any proprietary interest in any research reviewed by the IIRB, Inc. other than copyrights and patents without royalties.
7. Currently serve or have the potential to serve as an executive or director of any organization related to the review of studies by the IIRB, Inc.
8. Received or have the potential to receive any income from seminars, lectures or teaching engagements sponsored by any organization related to the review of studies by the IIRB, Inc.
9. Received or have the potential to receive any income from service on advisory committees or review panels by any organization related to the review of studies by the IIRB, Inc.
10. Received or have the potential to receive any compensation whose amount would be affected by the outcome of any research studies reviewed by the IIRB, Inc.
11. Received or have the potential to receive any financial compensation that requires disclosure to the sponsor or funding source of any research study reviewed by the IIRB, Inc.
12. Received or have the potential to receive any financial compensation in any research study reviewed by the IIRB, Inc. with value that cannot be readily determined.
13. Currently have or have the potential to have any other financial interest or affiliations with an organization that may interfere with the protection of study participants or the outcome of any research reviewed by the IIRB, Inc.

The following potential conflict of interest criteria applies to all investigators and key research staff:

1. Currently have or will potentially have any ownership interest, stock options, or other equity interest with a sponsoring organization greater than 5% of total equity.
2. Currently received or will potentially receive payments from a sponsoring organization that exceeds $10,000 in excess of study budget when aggregated for immediate family members in one year.
3. Currently have or have the potential to have a financial interest in a sponsoring organization that values exceeds $10,000 when aggregated for immediate family members in one year.
4. Currently have or have the potential to have any proprietary interest in a sponsoring organization, such as a patent, trademark, copyright, or licensing agreement.
5. Currently have or have the potential to have any proprietary interest in a sponsoring organization other than copyrights and patents without royalties.
6. Currently serve or have the potential to serve as an executive or director for a sponsoring organization.
7. Receive or have the potential to receive any income from seminars, lectures or teaching engagements from a sponsoring organization.
8. Receive or have the potential to receive any income from service on advisory committees or review panels by a sponsoring organization.
9. Receive or have the potential to receive any compensation whose amount would be affected by the outcome of a research study.
10. Receive or have the potential to receive any financial compensation that requires disclosure to a sponsor or funding source of a study.
11. Receive or have the potential to receive any financial compensation from a sponsoring organization of a study with value that cannot be readily determined.
12. Currently have or have the potential to have any other financial interest or affiliations with a sponsoring organization that may interfere with the protection of study participants or the outcome the research study.
13. Currently have or have the potential to have a financial interest that requires disclosure to the sponsor or funding source.
14. The research study is being conducted as a component part of a franchise relationship with a sponsoring organization.

Non-financial Conflict of Interest. Non-financial conflict of interest may exist when an individual serves dual roles, such as health care provider and investigator. Other interests such as publication, promotion or tenure, can also become conflicts of interest that may affect an individual's judgment. Membership in oversight committees such as the IRB as well as positions of authority may pose potential conflicts of interest. Any position that includes responsibilities for the review and approval of research projects or contracts other than his/her own may potentially affect the design of, decisions made

and/or action taken surrounding a specific study.

Financial and Non-Financial potential COI include Investigators, key research staff, IRB members, Consultants, IIRB, Inc. Managers, IIRB, Inc. Administrative Staff and their immediate family. See Glossary for definition of immediate family member.

KEY COMPONENTS OF THE PLAN

1. IIRB's definitions and thresholds for "conflicts of interest" and "significant financial interests" are available on the website and in the Investigator's Guidebook and serve as an educational resource for investigators.
2. Investigators are required to identify potential conflict of interest with every research study submission by completing the Site Questionnaire and if applicable Site Conflict of Interest and Disclosure Form.
3. The IRB assesses any investigator potential conflict of interest through the Research Evaluation Process.
4. IRB Members and Consultants have an awareness and understanding of what a conflict of interest entails and the processes involved through in-house training.
5. Individuals within the IIRB, Inc. organization, IRB Members, IRB Consultants are required to disclose annually and continuously update information about any potential conflict of interest.
6. IRB Members and Consultants will be queried by the Chair about potential COI at every IRB Meeting.

REVIEW AND MANAGEMENT OF "INTERNAL" POTENTIAL FOR COI

IRB members are independent consultants to the organization and generally are not actively engaged in the conduct of research, do not hold substantial amounts of stock, or receive any type of grants or honorarium. All members of the Board of Directors, Investigational Review Board (IRB), Mangers, Administrative Staff, and Financial and Human Resource Personnel will complete a Conflict of Interest and Disclosure Form on an annual basis.

The IOAG reviews any potential Internal COI that is identified, assesses these potential COI and recommends actions as appropriate. The IO may determine that further notification to the Board of Directors is warranted based on the relationship status of the individual with an identified COI with the IIRB, Inc.

It is the responsibility of the IRB Member to immediately identify any potential COI at the time that the research is presented for any action. The Chair, Vice Chair, or designee selected by the Chair or Vice Chair contacting the Consultants will ask the Consultant to disclose any potential COI prior to providing any consultation services.

When a potential COI is identified, the actions to be taken include, although may not be limited to following:

- If a member of the IRB is identified as having a potential COI with an

investigational study under review, this includes involvement as a clinical investigator, sponsor, monitor or coordinator and proprietary interest and/or equity interest (see definition of Financial/Non-financial Conflict of Interest), the individual that identified a COI may only be present at the meeting to answer questions, however, he or she will not participate in the vote and must leave the room.

- If an individual (i.e., Consultants and Investigators) that is identified as having a potential COI may be consulted on clinical investigations for clarification or be requested to attend the meeting. A consultant with a COI may only be present at the meeting to answer questions and must leave the room for deliberations and voting. Information about the COI will be disclosed to IRB members at the meeting and documented in the minutes.
- If Management or Administrative Staff have an identified potential COI they are not permitted to process documents for which there has been identified a potential COI.

REVIEW AND MANAGEMENT OF "EXTERNAL" POTENTIAL FOR COI

The Site Questionnaire includes protocol-specific questions regarding conflict of interest for the investigators, key personnel and their immediate families. These definitions are provided to the Investigator on the web site and are included in the "Investigator Guidebook". The Investigator must document and affirm full disclosure of any potential COI on the Conflict of Interest and Disclosure Form.

All documented potential COI are evaluated by the IRB. The IRB at the initial review of the research protocol, at the time of Continuing Review and if identified as a change in COI during the review period, will determine the following:

- Whether the conflict, financial or non-financial, affects the protections of research participants,
- Whether a conflicting interest might adversely affect the credibility of the HRPP Plan thus creating the appearance of conflicts of interest.
- Whether the conflict of interest might influence the outcome and results of the research study
- Whether a site visit by a representative of IIRB, Inc. is warranted.

If the IRB identifies a potential COI the IRB may select a management plan which may include:

1. Disclosure to subjects through the consent process
2. Modification of the research protocol or safety monitoring plan
3. Monitoring of research by independent reviewers
4. Disqualification of the conflicted party from participation in all or a portion of the research

5. Appointment of a non-conflicted Principal Investigator
6. Divestiture of significant financial interests
7. Severance of relationships that create actual or potential conflicts.
8. Prohibition of the conduct of the research under the oversight of the IIRB, Inc.

The IRB will document findings regarding the assessment of potential COI on the Board Evaluation portion of the Research Evaluation Form including the need for IRB action related to the potential COI.

Information regarding the potential COI and the management plan will be communicated to the Investigator. All identified potential COI must be addressed to the satisfaction of the Investigator and IRB prior to approval. The IRB has the final authority to determine whether the research with the potential COI and the management plan, allow the research to be approved.

See Internal Conflict of Interest and Disclosure Form and Site Conflict of Interest and Disclosure Form

PURPOSE

The purpose of the Site Evaluation Plan is to provide the IRB with a mechanism to conduct an 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 qualification to determine the competence of the Investigator to conduct the submitted research study. The Site Questionnaire provides the IRB with information about the 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.

SCOPE

Evaluation of the Site and qualifications and training of the investigator(s) is fundamental in determining if a research project meets regulatory criteria for approval. Each investigator under the oversight of the IIRB, Inc. is evaluated based on the information submitted in the Site Questionnaire(s) and all applicable supporting documentation. This process is conducted by reviewing the Site Questionnaire and includes information regarding the research environment, provides indications of expertise and regulation knowledge of the investigator(s) and staff, and includes the site's standard procedures for research activities such as recruitment and the consenting process. Evaluation of potential conflicts of interest is included in this process. A Qualified Screening Staff will review the Site Questionnaire(s) and all applicable supporting documentation for adequacy and completion prior to IRB review. The Qualified Screening Staff may determine that additional documentation is required prior to review by the IRB.

During the duration of the approval of a research study, the site is monitored by mechanisms listed in the Continuous Quality Improvement Program (CQIP) by reviewing unanticipated problems, serious and continuing non-compliance and suspension and termination. Based on these findings actions may be taken as outlined in the HRPP Plan under the Unanticipated Problems, Reports of Non-Compliance, and Suspensions and Termination sections.

Unanticipated problems are an indicator that additional site evaluation may be warranted.

RESPONSIBILITY

The Site Evaluation Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

See Attached Site Questionnaire Form and applicable addendums to the Site Questionnaire and applicable supporting documents.

RESEARCH EVALUATION PROCESS AND PLAN

HRPP PLAN ATTACHMENT 4

PURPOSE

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 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 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.

SCOPE

The research evaluation process begins with the information provided by the research site and is documented in the Site Questionnaire(s) and relevant supporting documents. The research evaluation process includes an assessment of the Site Questionnaire(s) with relevant supporting documents, research protocol, advertisement/recruitment material, and draft informed consent form.

RESPONSIBILITY

The Research Evaluation Process and Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

PROCESS

A Qualified Screening Staff will review the Site Questionnaire(s) and all relevant supporting documents and submission documents. The Qualified Screening Staff will use an electronic Research Evaluation Form (or hard copy of a Research Evaluation Form if the electronic version is not available) as a checklist to evaluate the research study submitted as well as the qualification of the investigator(s) and research facility. These findings will be documented on the Research Evaluation Form. At the completion of this portion of the process, the Qualified Screening Staff will determine if the submitted research study is accurate and complete for IRB review. The Qualified Screening Staff may initiate an inquiry for additional clarification or information from the Site. The Qualified Screening Staff will compile his/her findings and comments on the Board Evaluation portion of the Research Evaluation Form or separate supplemental documentation if the electronic versions of the Research Evaluation is not available. This documentation will be reviewed by the IRB to determine if the research study meets criteria for approval and will include the IRB's comments, findings, and final action. The convened IRB uses the Research Evaluation Forms to approve research undergoing initial review and continuing review. The IRB Members and expedited reviewers will use the Criteria for Approval Guidance Sheet when reviewing modifications to ongoing research. The IRB assessment will be documented on the Board Evaluation portion of the Research Evaluation Form. If the electronic Board Evaluation Form is not available, the IRB will document their findings on either a supplemental form outlining the criteria for approval or directly in the IRB meeting minutes. The completed Research Evaluation

Form including the Board Evaluation portion can be kept in either the hard copy study file, or stored in the Bizsuite database system.

During the duration of the study, modification to the research (i.e., Amendments, Revised Protocols) will be reviewed and the Research Evaluation Form will be reviewed to determine if the modification changes information on the Research Evaluation Form.

At the time of continuing review, a Qualified Screening Staff will review the electronic Research Evaluation Form from the initial review if it is available or the initial review documentation, make any changes necessary that were reported during the period in which the study was approved and that were reported on the Progress Report Form. In addition, the IRB will review the Research Evaluation Form including the Board Evaluation portion if available to determine if any of the criteria for approval has been modified, if additional verification from outside sources are required, and the approval period will be assessed and documented on the Research Evaluation Form or directly in the IRB meeting minutes.

UTILIZING THE ELECTRONIC RESEARCH EVALUAION FORM

The Research Evaluation Form is a two step process to evaluate the research site, investigator, and research study, and to assist the IRB in evaluating Criteria for Approval (see HRPP Plan). The Research Evaluation Form is an electronic checklist customized for each research study and research site that includes (1) research evaluation portion; and (2) board evaluation portion. The research evaluation portion of the study is completed by a Qualified Screening Staff and includes questions on the research setting, protocol, informed consent process, and informed consent elements. This portion of the process is designed to generate specific questions for specific study types (e.g., phase 1, device, minimal risk) and for specific populations (e.g., diabetic, children, renal impaired). Each question is designed to generate additional questions based on the answers given. With each question, the Qualified Screening Staff reviewing the study prior to IRB review will have the option to make comments for the IRB's review. These comments are generally areas that do not clearly meet IIRB, Inc's requirements, or that need special attention by the IRB. The Qualified Screening Staff also has the capability of recommending standard notes for the approval letter (see Sample Notes for Approval Letter).

The board evaluation portion of the form addresses each criteria of 21 CFR 56.111 and 45 CFR 46.111 Each question of the research evaluation portion is linked to one of the Criteria for Approval and is listed on the board evaluation portion to assure that the board specifically addresses each criteria and provides documentation of their findings. The answers, comments, and notes included on the research evaluation portion will generate the board evaluation portion of the Research Evaluation Form. The board evaluation portion includes the areas of concern, recommendations, and findings identified by the Qualified Screening Staff. The IRB will review both the research evaluation portion and the board evaluation portion of the Research Evaluation Form at the time the study is being evaluated for IRB approval.

The following are codes identified on the Research Evaluation Form:

A	Section A of Board Evaluation “Risks to Subjects are Minimized”
B	Section B of Board Evaluation “Risks are Reasonable in Relation to Anticipated Benefits”
C	Section C of Board Evaluation “Section of Subjects is Equitable”
D	Section D of Board Evaluation “Informed Consent is Sought from Each Subject”
E	Section E of Board Evaluation “Informed Consent is Appropriately Documented”
F	Section F of Board Evaluation “Data Collected is Monitored to Ensure Subject Safety”
G	Section G of Board Evaluation “Privacy and Confidentiality of Subjects is Protected”
H	Section H of Board Evaluation “Additional Safeguards are Included for Vulnerable Populations”
FN	Section File Notes of Board Evaluation
O	Other Section of the Board Evaluation

The codes indicate the following:

SS: Default for single site review
MST: Default for multi-site review when the protocol and template ICF are being reviewed (not site review).
MSS: Default for additional sites as modifications for previously approved research protocol.
Is not for minimal risk: questions indicated with this code do not appear for minimal risk studies.

If the electronic Research Evaluation Form (including research evaluation portion and board evaluation portion) is not available, the Manager will use a supplemental checklist for pre-screening the study and provide this documentation to the IRB for review. The IRB will review the study in the same way as if an electronic Research Evaluation Form was used, but document their review of the criteria for approval in the IRB meeting minutes rather than the board evaluation portion of the Research Evaluation Form.

See Attached Research Evaluation Form (includes research evaluation portion and board evaluation portion), Sample Notes for Approval Letter, and Criteria for Approval Guidance Sheet.

PURPOSE
The purpose of the IIRB, Inc. Website Overview is to serve as a synopsis, purpose, and rationale of each section that is contained within the www.iirb.com website.

SCOPE
The IIRB, Inc. has developed an innovative user friendly website to provide information about IIRB, Inc. to the public, assist clients with submitting documents for review, providing education to investigators and research subjects, and for communicating with clients and research subjects. The website also serves as a communication and resource center for IRB members.

The IIRB, Inc. homepage consist of 4 main sections including; About IIRB, Inc., Sponsors/CROs, Investigators/Research Staff, and Research Participants, and 4 subsections; Education, Contact, Login, and Search.

RESPONSIBILITY
The IIRB, Inc. Website Overview is approved by the Board of Directors on an annual basis with interim changes to the website initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG.

MAIN SECTIONS

About IIRB, Inc.
The About IIRB, Inc. section of the website serves as an overview of the IIRB, Inc. This section of the website includes the IIRB, Inc. mission statement, a brief history of the organization, compliance statement, and accreditation status. In addition, this portion of the website includes recent findings from the U.S. Food and Drug Administration (FDA), information on services, guidelines for submitting research studies for review. For more information regarding the About IIRB, Inc. section see www.iirb.com.

Sponsors/CROs
The IIRB, Inc. has an entire section of the www.iirb.com website to provide information and guidance to Sponsors/CROs. The Sponsors/CROs section of the website includes information for submissions, list of services, use of forms for submissions, IRB Roster, Fees and Meeting Calendar, information on Human Research Protection (HRP) training, and links to helpful references and regulatory agencies. For more information regarding the Sponsors/CROs section see www.iirb.com.

Investigator/Research Staff
The IIRB, Inc. has an entire section of the www.iirb.com website to provide information and guidance to Investigators/Research Staff. The Investigators/Research Staff section of the website includes information for submissions, list of services, use of forms for submissions, IRB Roster, Fees and Meeting Calendar, information on Human Research Protection (HRP) training, and links to helpful references and regulatory agencies. For more information regarding the Investigators/Research Staff section see www.iirb.com.

Research Participants

The IIRB, Inc. has dedicated an entire section of the www.iirb.com website to provide potential and current subject with information regarding their rights as research subjects, questions to ask before and after they decide to participate in a research study, key research terms, and additional resources with their relative links. In addition, the Research Participant section includes an mechanisms for subjects to contact the IIRB, Inc. if they have any questions, comments, complaints, or if they wish to speak to someone other that the investigator or research team. For more information regarding the Research Participant section see www.iirb.com.

SUBSECTIONS

Education

The Education section supports the efforts listed in the Training and Education Program. This section provides additional resources to clients, including information related to HRP training, newsletters to keep clients informed, Investigator's Guidebook and provides information on webinars.

Login

The Login section of the website provides secure access to authorized Sponsors/CROs, Investigators/Research Staff, IRB Members, and IIRB staff. IRB Members use the website as a communication venue and portal system for providing study materials to IRB Members for review prior to an IRB Meeting. The portal system can be accessed from remote locations, and provides convenience for accessing the study related documents prior to IRB review. The IRB Member section is password protected so that only IRB Members have access to the study related documents. In addition, the IIRB, Inc. will be notified that all recipients of the study documents receive and are able to read the material. Sponsors, CROs, Investigators, and Research Staff can access a secured portal to review approval documents.

Contact Us

The Contact Us section of the website serves as a mechanism for sponsors, CROs, and investigators can contact the IIRB, Inc. with question or comments. Research Participants can contact the IIRB, Inc. through the Research Participant section of the website in which they can choose to submit question, comment, or complaint anonymously. For more information regarding the Contact Us section see www.iirb.com.

Search

The search function of the website allows visitors to locate information by entering a key word. The search function locates each place that the key word is located on the website for more accessible information.

PURPOSE
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 the Investigator conducting research studies involving humans.

SCOPE
The IIRB, Inc. refers all Investigator's under the oversight of the IIRB, Inc. to the Investigator's Guidebook located on the website. The most recent version is maintained on the www.iirb.com website, and may provide copies to investigators and key research staff at site visits. The Investigator's Guidebook contains information for submitting new research studies including information addressing how to complete the Site Questionnaire. In addition, the Investigator's Guidebook contains sample language for informed consent process procedures, advertisements/recruitment, and receptionist screening script that can be utilized in the Site's development of standard operating procedures. The Investigator's Guidebook also provides investigators with useful resources for regulatory compliance and guides them in submitting potential unanticipated problem, and serious or continuing non-compliance and changes to research during the duration of the study.

RESPONSIBILITY
The Investigator Guidebook is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

See Investigator's Guidebook

IRB MEMBERSHIP DOCUMENTATION PLAN

HRPP PLAN ATTACHMENT 7

PURPOSE

The IRB Membership Documentation plan documents IRB member roles and qualifications.

SCOPE

The IRB Membership Roster documents the IRB Membership in accordance with 21 CFR 56.107 and 45 CFR 46.107 and qualifications and is posted on the website. A summary is maintained that documents compliance with regulatory requirements and includes the name 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. Each IRB Member's qualifications are filed in their Training and Education File.

Updated IRB Membership Rosters will be provided to OHRP to update IIRB, Inc.'s registration with OHRP. The IO or member of the IOAG will be responsible for reporting changes to IRB Membership Roster to OHRP.

RESPONSIBILITY

The IRB Membership Documentation Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis.
Prior to changes by the IO, these changes will be evaluated by the IOAG.

See IRB Membership Roster.

CONTINUOUS QUALITY IMPROVEMENT PROGRAM (CQIP) PLAN

HRPP PLAN ATTACHMENT 8

PURPOSE

The HRPP Plan includes identifying opportunities to maximize compliance with IIRB, Inc. policies and procedures and provides opportunities for continuous quality improvement. The CQIP Plan is intended to ensure that the HRPP plan and the efforts made by the Organization, IRB, and investigators under the oversight of the IIRB, Inc. are performing in such a way to meet the goals of the HRPP Plan and to provide optimal human research protection.

SCOPE OF CONTINUOUS QUALITY IMPROVEMENT PROGRAM (CQIP) PLAN

The IIRB, Inc. is committed to implementing ongoing monitoring mechanisms to assure that the actions of the IRB are carried out accurately, in a timely manner, and to support the IRB in its function. The HRPP Plan includes identifying opportunities to continuously improve the operations of IIRB, Inc. and compliance with the HRPP Plan. The CQIP Plan includes a Continuous Quality Improvement Program (CQIP) for continuous monitoring of key quality indicators. In addition, the CQIP Plan outlines how the findings are reported throughout the Organization. The CQIP Plan is intended to be integrated with the Training and Education Program in order to be a source for identifying areas of need for continuing education, and to be a source for identification of areas that may need procedural improvement and areas of noncompliance. The CQIP also includes internal audits of the Organization and external audits of a portion of the investigators under the oversight of the IIRB, Inc. to ensure compliance with the IIRB, Inc. HRPP Plan.

The CQIP Plan integrates Internal and External Audit Findings and Procedures into IIRB, Inc.

RESPONSIBILITY

The IOAG oversees the development and implementation of the CQIP Plan. The Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB if appropriate.

CONTINUOUS QUALITY IMPROVEMENT PROGRAM (CQIP)

The CQIP includes ongoing review of quantitative key quality indicators, and periodic qualitative assessments of staff and the IRB to evaluate compliance with written policies. Additional monitoring can be instituted by the IOAG on a periodic or ongoing basis at any time.

Quantitative Key Quality Indicators

Key quality indicators include, monitoring of corrected report rates, study file documentation compliance, Subject, Sponsor, and CRO contacts, and IRB indicators of compliance with subpart regulatory requirements. Key quality indicators for Training and Education include new information in-services, review of QI findings, and areas of

procedural improvement. The ongoing key quality indicators are identified below. Each key quality indicator includes the purpose, and process. The IO may add or remove key quality indicators listed in the table below, as deemed necessary.

The program includes active "Peer Review" and reporting of findings on a monthly basis at Staff Meetings and provides a foundation for the Training and Education Program. The CQIP includes mechanisms to integrate findings with IRB actions through multi-disciplinary monitoring and through the Training and Education Program. Periodic reporting of ongoing monitoring assures timely communication.

A Member of the IOAG or designee will collect the data for each key quality indicator as indicated in the process section of the CQIP Plan. This information will be documented on the CQIP Calendar as indicated in the process section of the CQIP. Key quality indicators are reported to the IRB and IOAG on a quarterly basis, to the staff on a monthly basis and to the Board of Directors on a semiannual basis.

Qualitative Assessments

In addition, to the quantitative key quality indicators, periodic qualitative assessments will be conducted. The following outlines these qualitative assessments.

Monthly Assessment

A monthly assessment is conducted by the Quality Control Specialist or designee under the oversight of the Chief Operating Officer. Findings from the monthly assessment will be documented on the Continuous Quality Improvement Monthly Assessment form and reported to IOAG and IRB as deemed relevant by the Chief Operating Officer.

Area of Assessment (1): Review at least 8 research study files to assure retention of appropriate documentation and consistent organization of the IIRB, Inc. file according to current HRPP Plan. The sample of new research study files reviewed should accurately reflect a sample from each Project Leader.

Area of Assessment (2*):* Review MWFs for each project leader to verify 1) items on MWF are in the appropriate set of IRB Meeting Minutes, or Expedited Agenda, as applicable, 2) each item in a specific set of minutes in on a MWF.

Monthly IO Assessment

A monthly assessment is conducted by the IO or designee. Findings from the monthly IO assessment will be documented on the Continuous Quality Improvement Monthly IO Assessment form and reported to IOAG and IRB as deemed relevant by the IO.

Area of Assessment (1): Review at least 2 sets of IRB Meeting minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include 1) assessing the documentation surrounding the discussion of the criteria for approval for initial and continuing reviews, 2) assessing that a quorum was met and maintained, 3) assessing the documentation to verify that additional safeguards in the enrollment of children or pregnant women as outlined in Subpart B and D were documented, 4) verifying that the IRB made a determination if a reported problem in research is an unanticipated problem or serious or continuing non-compliance, 5)

evaluating if members with a conflict of interest recused themselves from the discussion/vote, as applicable.

Area of Assessment (2): Review at least 10 items reviewed under expedited review procedures to verify that the review was conducted under the expedited review procedures listed in the HRPP Plan and appear to meet the criteria for expedited review.

Annual Assessment

An Annual Assessment is conducted by the IO or designee. Findings from the Annual Assessment will be documented on the Continuous Quality Improvement Annual Assessment form and reported to IOAG and IRB as deemed relevant by the IO.

Area of Assessment (1): Assessment of the compliance and documentation of policies and procedures by using the FDA Checklist for Independent IRBs.

Area of Assessment (2): Assessment of IIRB, Inc. employees and IRB Member Training Files for accuracy, completeness, and to ensure that all license/certificates are current.

QUALITY IMPROVEMENT THROUGH ACTION REPORT

A QI finding may warrant a "QI Through Action Report". The "QI Through Action Report" will include the source, observations, action, follow-up action, and an option for a follow-up verification. The IO will review the "QI Through Action Report" and determine if a verification of the follow-up action is warranted. The "QI Through Action" may be reported to the IRB at the next IRB meeting, the staff through utilization of the Internal Communication Exchange (ICE) system, or reported at the next IIRB, Inc. Staff Meeting as appropriate.

INTERNAL AUDITS

Internal audits are audits of the services provided by the IIRB, Inc. and are conducted by individuals that are not employees of the IIRB, Inc. The IIRB, Inc. is audited by external sources such as regulatory agencies (i.e., FDA, OHRP, and EPA), accreditation agencies (i.e., AAHRPP), due diligence audits by Sites, Sponsors, or CROs, or by hired outside consultants. These audits may provide opportunities to improve the way the IIRB Inc. provides services or require changes to the way that the Organization provides services.

The IO may determine that an internal audit by an external auditor or consultation regarding the services provided by the IIRB, Inc. is warranted. The Organization has the resources to conduct an internal audit, but may for any reason determine that additional expertise by an external consultant may be useful.

All External Auditors will be required to provide personal and professional identification and complete the IIRB, Inc. confidentiality documents.

Clinical Investigators, CROs and Sponsors may request access to files pertinent to their studies, the HRPP Plan, Work Instructions (WI), IRB Membership Rosters, and any other relevant documentation. The request must be provided in writing and include

areas of review and requested information. Request will be reviewed by the IO. The IO may decline a request for information by a Sponsor or independent monitor for business confidentiality purposes.

If any deficiencies are noted in the review, a QI Through Action Report may be developed by a member of the IOAG or designee and approved by the IO. A member of the IOAG or assigned designee will/may be responsible for implementing the QI Through Action Report, and these results will be evaluated by the IO and IOAG as necessary.

EXTERNAL AUDITS

External audits are audits that are conducted by the IIRB, Inc., or a consultant acting on the behalf of the IIRB, Inc., Investigators, of Sites, CROs or Sponsors. The External Audits include Site Compliance Visits, Directed Audits or Massachusetts Required Site Visits. Site Compliance Visits are periodically scheduled and are intended to assess Investigator and Site compliance with federal, state, and local law, IIRB, Inc. policies and may include review of research being conducted under the oversight of IIRB, Inc.

Review activity may include observing the consent process, identifying of areas for improvement; making recommendations based on existing policies and procedures and also providing education regarding the Site's HRPP. Directed Audits of Sites where IIRB Inc. approved research studies are conducted may be in response to identified unanticipated problems, serious or continuing non-compliance or enrollment of vulnerable populations. Site Compliance Visits may be selected based on the following criteria: high-volume site, high-risk study, significant changes in research staff or location, reported problems, requested additional education, or any other relevant criteria. Massachusetts Required Site Visits are conducted according to Massachusetts State Law.

Activities of auditors during Directed Audits and Site Compliance Visits may include:

a) Requesting progress reports from researchers;
b) Examining investigator-held research records;
c) Contacting research subjects;
d) Observing research sites where research involving human research subjects and/or the informed consent process is being conducted;
e) Auditing advertisements and other recruiting materials as deemed appropriate by the IIRB, Inc.;
f) Reviewing projects to verify from sources other than the researcher that no unapproved changes have occurred since previous review;
g) Monitoring conflict of interest concerns to assure the consent documents include the appropriate information and disclosures;
h) Monitoring HIPAA authorizations;
i) Conducting other monitoring or auditing activities as deemed appropriate by the IIRB, Inc.
j) Educational slide show may be provided to the investigator(s), regulatory affairs designee, and any key research staff on the role and history of the IIRB, Inc.

The results of external audits and compliance reviews including reports of

noncompliance and/or recommendations are reported to the IO within 2 weeks of the site visit. The IO will review the findings from the audit and determine whether reporting to the IOAG and IRB is required. A member of the IOAG will communicate findings from the audit to the Site, Investigator, and Sponsor/CRO if necessary. If significant findings are identified, a member of the IOAG will remain in communication with the audited entity until resolution of the finding(s).

If an audit or review identifies serious unanticipated problems or serious or continuing non-compliance, immediate reporting and action by the IRB is required, and may include suspension or termination of the research study. The IRB will determine if any deficiencies are noted in the review and a corrective action plan will be requested and follow up conducted as warranted. Findings from the external audit may also be incorporated in the CQIP.

The IO will review the findings of all external audits and determine if any opportunities to improve internal procedures or implement more effective human research participant protection procedures are identified. If any are identified, the IO will take action as identified in the HRPP Plan to implement these procedures. The IRB will be notified of any relevant findings. The IO or designee will prepare a response to the external auditor, if necessary.

KEY QUALITY INDICATORS

Indicator	Purpose	Process
Volume Indicators (i.e., # initial approval, #items reviewed through expedited review procedures, # additional sites, #Amendments and Administrative Changes including ICF changes, # of Unanticipated Problems, # revised Form FDA 1572, # continuing reviews, # study completion, # other actions, and # IRB meetings held)**.**	The collection and display of the volume indicators is intended to provide base-line information regarding the activities of the IIRB, Inc. for planning and comparison purposes.	The information is collected through the IRB database system and summarized.
# of items not mailed by Friday for Tuesday IRB Meeting or mailed by Tuesday for Thursday IRB Meeting	The collection and evaluation of the volume indicators is intended to provide an assessment of overall work flow, and adequacy of resources available to ensure that document are mailed within 3 days of an IRB Meeting.	The information is collected on a weekly basis by the Assessment of Workflow
Staff Key Quality Indicators	**Purpose**	**Process**
# corrected report	To identify opportunities to improve processes to decrease opportunities for error. Identify opportunities for staff education.	Occurrence and QI Reporting Review of Memorandum file to identify when corrected reports occur. Reporting from all other QI sources; i.e., open file review, closed file review,

		etc.
% compliance open file review	To identify and correct errors on an ongoing basis. To identify opportunities to improve processes to decrease opportunities for error. Identify opportunities for staff education	Based on the number of new studies approved (initial review), an equivalent number of open files will be randomly selected for QI Review; including: File Completeness, Document Accuracy, and Minutes Accuracy
% compliance closed file review	To identify and correct errors on an ongoing basis. To identify opportunities to improve processes to decrease opportunities for error. Identify opportunities for staff education	All closed files will be reviewed to verify that all correspondence is accurately recorded in the minutes
# subject complaints/Follow up calls	To actively intervene and serve as an advocate for research subjects and to follow up on any problems or questions. Identify site related-problems for follow up and identify internal opportunities for system-wide improvement.	Implement subject complaint policy for immediate attention to subject calls.
# Quality Improvement through Action	To be proactive in the follow-up of issues, suggestions or concerns and to follow up on any problems or questions. Identify internal opportunities for system-wide improvement.	Document through use of QI through Action Report and conduct follow up as warranted.
# inservice completed - Staff	Inservice education is intended to compliment the Quality Improvement process through proactive education, review of changes to policies and procedures, and Forms. In addition, the results of QI monitoring will be incorporated into the inservice program.	Document inservices completed by staff using the ICE system.
# WI updated/revised	To improve accuracy and consistency through on-going review, update and implementation of WIs	Document new and revised WIs.
% compliance Minutes Accuracy	To concurrently verify accuracy of minutes in addition to closed file review.	All new studies will be verified in the minutes and a random sample of items for action will be verified for percent compliance calculation.
Error rate	To identify the overall error rate including number of mistakes,	Identify the total number of mistakes and corrections.

	and number of corrections	
Other Key Quality Indicators	**Purpose**	**Process**
Iron Mountain Problems or Issues	To document the number of times the IIRB, Inc. had problems or issues that may impact procedures or confidentiality including reports of lost boxes, inability to locate boxes, and delays in retrieving boxes that impact procedures.	Track the number of issues that impact procedures or confidentiality as the events occur and document the findings for each month on the calendar.
IRB Key Quality Indicators	**Purpose**	**Process**
# Site/Sponsor Protocol revisions required for subject safety (a) Risk Information (b) Study Design (c) Study Procedures (d) Blood Volume (e) Other (as applicable)	To document Screening and IRB actions taken to protect the rights of Research participants	Documents IRB interventions and summarizes based on issues identified
# Tabled for clarification (a) Risk Info. (b) Stipend missing or requires clarification (c) Study Design (d) Study Procedures (e) Blood Volume (f) Other	To document IRB actions taken to protect the rights of Research participants	Documents IRB interventions and summarizes based on issues identified
# of Referrals for additional scientific consultation	To document IRB actions taken to protect the rights of Research participants	At the time of protocol screening and at the time of presentation to the IRB, assessment of the need for additional consultation is evaluated and documented to determine trends in requests for additional expertise.
# inservice completed - IRB	Inservice education is intended to compliment the Quality Improvement process through proactive education, review of changes to regulations and research environment. In addition, the results of QI monitoring will be incorporated into the inservice program.	Document inservices completed by IRB as documented in the Board Training Files.

See attached Continuous Quality Improvement Monitoring Calendar, Continuous Quality Improvement Monthly Assessment form, Continuous Quality Improvement Monthly IO Assessment form, and Continuous Quality Improvement Annual Assessment form

TRAINING AND EDUCATION PROGRAM PLAN

HRPP PLAN ATTACHMENT 9

PURPOSE

The purpose of the Training and Education Program 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 Organizational Mission.

SCOPE

The Training and Education Program Plan includes both Internal and External Training and Education components. Internal Training and Education includes mechanisms for the orientation, training and education of IRB Members, Manager, and Administrative Staff. The Training and Education Program is designed to integrate with the Continuous Quality Improvement Program (CQIP) Plan and the Conflict of Interest Plan.

The External Education and Training component of the Plan includes the assessment of the Training and Education of Investigators and key staff. The External Training and Education Program is designed to integrate with the Research Evaluation Process and Plan.

Educational outreach to research participants is addressed within the Research Participant Outreach Program Plan. The Training and Education Program includes a documentation component.

RESPONSIBILITY

The Training and Education Program Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

EXTERNAL TRAINING – INVESTIGATOR AND KEY STAFF

The IIRB, Inc. requires all Principal Investigators under the oversight of the IIRB, Inc. to have HRP training such as Collaborative Institutional Training Initiative (CITI), NIH Human Participant Protections Education, OHRP Training Modules or other Professional Society Training (DIA, SOCRA, ACRP). For Principal Investigators with no HRP training or with less than 1 year experience in research involving humans, IIRB, Inc. requires these investigators to complete a basic HRP training through CITI. The IO may decide to waive the requirement for HRP Training based on history of human research studies completed and history of compliance observed with studies conducted under the oversight of the IIRB, Inc

The IIRB, Inc. accomplishes continuing education for Human Research Protection (HRP) to investigators through offering an opportunity to complete HRP modules through CITI HRP training. Other forms of HRP training are evaluated in the Site Evaluation Plan and are reported on the Site Questionnaire. In addition, the IIRB, Inc. provides all investigators with an Investigator's Guidebook and has dedicated a portion

of the website for investigators to gather information on regulatory requirements, instruction for submissions conducting safe research, and the expectation of the IRB. The IIRB, Inc. has also developed forms to assist investigators in submitting information to the Organization, and reporting unanticipated problems in ongoing research. The IIRB, Inc. provides feedback on modifications made by the IRB to the submitted informed consent form and recruitment material to further educate the Investigator about the requirements of the IRB.

Additional mechanisms to provide education to sites is availability of consultation with IRB Chair and Vice Chair and other staff, site visits, workshops, teleconferences and other communication processes.

In the case of an Investigator that is submitting a protocol for the first time or an investigator who may not be well-versed in the protocol submission procedures, individualized IRB consultations can be arranged.

The IO or designee will evaluate the effectiveness of the HRP trainings offered to Investigators based on Investigator conduct throughout the study (i.e., unanticipated problems, subject complaints, and non-compliance) on at least an annual basis or as necessary. The IOAG may perform evaluation of the effectiveness of the HRP trainings offered, but final evaluation will be determined by the IO.

INTERNAL TRAINING - IRB MEMBER

The purpose of this IRB training is to ensure that IRB members have an awareness and understanding of all the various requirements of their review and role in the protection of human research participants. In order to fulfill this requirement, the IIRB, Inc. has developed and implemented a comprehensive training and education program which encompasses an initial orientation period, periodic assessment of skills and expertise, and continuing education.

Orientation Period

Prospective new IRB Members will provide a copy of their CV and their license (if applicable) to the IRB Chair and IO for review and verification of qualifications for membership. Newly appointed IRB Members will be required to complete an in-service training program which is documented by completion of the Orientation Checklist. This training includes:

- Position Overview (e.g., expectation, workflow, conflict of interest and confidentiality policies)
- IRB Meeting Procedures (e.g., submission process, review process prior to and during IRB meeting, criteria for approval, review or problems in research)
- Education & Training (e.g., initial and continuing education requirements)
- HRPP Plan (e.g., review of HRPP Plan and Attachments)
- Work Instructions (e.g., purpose, overview, relationship to HRPP Plan)
- Organization Procedures (e.g., data security and disaster plan)
- Other training relevant to position

IRB Members also received training on federal regulations (21 CFR 56, 45 CFR 46, 21

CFR 50) and FDA information Sheets and documented in their Training File. In addition, IRB Members will complete web based training modules on HRP through CITI. Confirmation of training and understanding will be documented on the IRB Training and Education Form and filed in their individual training file.

Based on the qualifications of the new IRB Member and position to be held, the IRB Chair may determine that new IRB Members should be assigned a field-related current IRB Member to serve as a mentor to provide guidance to a new IRB Member based on an evaluation of the past experience of the new IRB Member. As a mentor, the current IRB Member will welcome the new IRB Member, inform the new member of upcoming meetings and offer to accompany him/her, schedule a meeting with the new member prior to IRB meeting to review processes and procedures, assure that he/she becomes familiar with the resources available, assist the new member in applying federal criteria and ethical principles in reviewing protocols, devote time to explaining special review circumstances such as research involving vulnerable populations, and review the current IIRB, Inc. submission forms and discuss how these are reviewed by the IRB.

New IRB Members will be given a 6 month time period in which they must have completed all of the Initial CITI Modules. Documentation of training is filed in each IRB Member's Training and Education File.

Periodic Assessment of Skills and Expertise

The IIRB, Inc. is dedicated to ensuring that the IRB has the appropriate scientific and scholarly expertise when reviewing research for the protection of research participants. To fulfill this requirement, the IIRB, Inc. periodically assesses the skills and expertise of the each IRB Member individually as well as the cumulative IRB.

On an annual basis, the Board of Directors evaluates the following:

- Member attendance to scheduled IRB Meetings
- Member continuing education and training
- Member CITI Training Requirements
- Current license or certificates
- Member compliance with HRPP Plan
- Demonstrates understanding of Regulations
- Adheres to Policies & Procedures
- Demonstrates positive and supportive attitude
- Respect of other IRB Members
- Performs in other capacities when needed
- Familiarity with review process and forms

Prior to each scheduled IRB Meeting, the Chair and Vice Chair will review the items on the agenda for review to ensure that the IRB has appropriate expertise. If additional expertise is required, the procedures listed in the Consultants section of the main HRPP Plan will be followed.

Continuing Education

The continuing of education of all IRB members is vital to stay current with relevant informed within the industry as well as regulatory guidance. The IIRB, Inc. maintains memberships with scholarly publications, professional societies, and industry forums and received periodic email updates from regulatory agencies in order to remain current with provisions for human research protection. The IRB utilizes these sources in the continuing education of IRB Members as well as other magazine/newspaper articles and current events. The members of the organization and IRB may determine when continuing education is warranted and may suggest a topic area to members of the IO and CEO. IRB members are also encouraged to provide continuing education related to their specific expertise (i.e., legal concerns, new medical standards, etc.). In addition, indicators and findings from the processes outlined in the Continuous Quality Improvement Program Plan will also present opportunities for continuing education. The organization also enrolls in periodic webinars to further provide up to date insight related to human research protection.

New information and regulations will be brought to the attention of the IRB Members as they are identified and applicable. These training sessions will be documents on each IRB Member's Board Training and Education Form.

The organization maintains a library of references specifically for IRB Members which include references such as:

- Federal Regulations (FDA, OHRP, EPA) including electronic access to CFRs
- ICH Guidelines
- Ethical Documents (Belmont Report, Nuremberg Code, Declaration of Helsinki)
- FDA Information Sheets
- Amdur, R. (2007). *Institutional Review Board: Member Handbook.*
- Amdur, R. & Bankert, E. (2006) *Institutional Review Board: Management and Function.* Second Edition.
- Scholarly Publications
- PDR Reference Manuals
- Other reference material

The organization also maintains a centrally located bulletin board that is dedicated to providing updated/new regulations, guidance, and articles pertaining to human research protection. Information on the HRP bulletin board is updated as new information becomes available.

In addition, all IRB Members are required to complete refresher modules through CITI every 3 years. The organization will also provide support to send as many IRB Members as possible to attend relevant HRP conferences (e.g., AAHRPP, PRIM&R, NAIM, NIH, or SOCRA).

Additional Training for Chair & Vice Chair

In addition to the training requirements listed above, individuals being trained for the Vice Chair position are required to complete the Vice Chair in Training Checklist. The

Vice Chair in Training Checklist is a custom designed training program geared to prepare the individual for the Vice Chair position. In doing so, there training consist of a series of skills acquired and evaluations throughout the program. The program is monitored by the current Chair, Vice Chair, and IO to ensure that the individual is obtaining the necessary expertise to serve as the Vice Chair. The program includes:

- Position Overview (e.g., expectation, workflow, conflict of interest and confidentiality policies)
- Ethical & Regulatory (e.g., ethical principles of the Belmont Report and Nuremberg Code, federal regulation, and guidance documents)
- IRB Meeting Procedures (e.g., submission process, review process prior to and during IRB meeting, criteria for approval, review or problems in research)
- Expedited Review Procedures and IRB reporting
- Other training relevant to position including summarizing the salient issues to identify consensus and conduct the meeting using Robert's Rules of Order

Individuals being trained for the Chair position that are currently serving as the Vice Chair will complete the following trainings:

- While serving as the Vice Chair, the individual will chair meetings in the present of the current Chair so that the Chair can provide guidance in chairing a given meeting.
- The IRB will periodically assess the performance of the Vice Chair in training and provide feedback on areas of improvement.
- Correspondence to the Investigator/Sponsor indentifying issues or concerns of the IRB will be developed and reviewed in collaboration with the current Chair, to ensure that the documentation adequately represents the IRB.
- Participate in teleconferences as applicable in discussing actions necessary to eliminate immediate risks to participants, and guidance to Investigators/Sponsor related to unanticipated problems in research involving risks to subjects or other, or events of serious or continuing non-compliance.
- Assist clients with initial submission to meet the expectations of the IRB and regulatory requirements.
- Assisting current Chair in taking immediate action to address the safety of subjects and calling an unscheduled meeting of the IRB.

The organization has the following expectation for the Chair and Vice Chair position:

- The Chair is responsible for overall assurance that the actions of the IRB are consistent with the Human Research Participant Program Plan (HRPP Plan). The Chair will ensure that the IRB is structurally sound, understands its role and fulfills its responsibility of protecting the rights and welfare of human subjects who take part in research under the oversight of Independent Investigational Review Board, Inc. He/she will chair IRB meetings and see that the functions of the IRB effectively meet organizational goals, objectives, and compliance with the HRPP Plan as well as federal regulations. This position requires strong leadership skills with a firm understanding of compliance requirements of all research related federal regulations governing human subject research. Regulatory requirements include, but are not limited to: FDA, DHHS/OHRP, GCP/ICH, and EPA.
- The Vice Chair is responsible for fulfilling the role of the Chair in the Chair's

absence or when applicable. The essential functions of the Chair will be fulfilled by the Vice Chair in the absence of the Chair. The Vice Chair is responsible for overall assurance that the actions of the IRB are consistent with the Human Research Participant Program Plan (HRPP Plan). The Vice Chair will assist the Chair in ensuring that the IRB maintains appropriate expertise, understands its role and fulfills its responsibility of protecting the rights and welfare of human subjects who take part in research under the oversight of Independent Investigational Review Board, Inc. He/she will chair IRB meetings as applicable and see that the functions of the IRB effectively meet organizational goals, objectives, and compliance with the HRPP Plan as well as federal regulations. This position requires strong leadership skills with a firm understanding of compliance requirements of all research related federal regulations governing human subject research. Regulatory requirements include, but are not limited to: FDA, DHHS/OHRP, GCP/ICH, and EPA.

In order to fulfill the expectation listed above, individuals must have the following qualifications to be considered for the Chair or Vice Chair position:

- Minimum of a Bachelor's Degree or RN with 3 to 5 years related experience and/or training.
- A full time employee with at least 3 years experience at the organization.
- Extensive knowledge and experience in the areas of regulatory compliance and research activities.
- Extensive knowledge of the HRPP Plan.
- Excellent leadership skills.
- Demonstrates effective verbal and written communication skills.
- Excellent interpersonal skills to effectively build and guide teams.
- Ability to identify problems, collect data, establish facts and draw valid conclusions by way or fact finding.
- Ability to present facts and recommendations effectively.
- Excellent organizational skills with great attention to detail.
- Exceptional time management and ability to handle multiple projects effectively.
- Must have knowledge of computer software applications in Microsoft Word, Excel, Outlook and the IRB database system.
- Ability to analyze medical/research data and statistics.
- Must have attended at a minimum of 15 IRB meetings as an IRB Member.
- Must have conducted a comprehensive review of a variety of submissions under different regulatory requirements for new research or ongoing research and present submission and findings to the IRB. Submissions should include 1) new submissions, 2) continuing review, 3) unanticipated problems involving risks to participants or others, 4) serious and/or continuing noncompliance, and 5) modification that do not meet criteria for expedited review.
- Must have completed all modules for IRB Members through the Collaborative Institutional Training Initiative (CITI) Human Research Protection Training.
- Must have completed the HRP Training Assurance modules through Office of Human Research Protection and National Institute of Health Protection Human

Research Participants or be a Certified IRB Manager (CIM) or Certified IRB Professional (CIP).

The Board of Directors is responsible for the selection and appointment of IRB Members to serve as the Chair and Vice Chair. Individuals that are not deemed to have the appropriate expertise and experience cannot be selected for consideration for these positions.

INTERNAL TRAINING - MANAGERS AND ADMINISTRATIVE STAFF

The purpose of this Manager and Administrative Staff training is to ensure that Managers and Administrative Staff have the appropriate training to support the function of the IRB and organization. In order to fulfill this requirement, the IIRB, Inc. has developed and implemented a comprehensive training and education program which encompasses an initial orientation period, periodic assessment of skills and performance, and continuing education.

Orientation Period

All new Managers and new Administrative Staff will receive an employee orientation during their first weeks of employment. The orientation will include a review of the HRPP Plan and Work Instructions. This orientation may also include a tour of the facility personnel policies, organizational purposes, regulatory requirements/references, website, computer files, email system, filing system, phone system, key client information, study files, and forms, and IIRB, Inc. computer system. The Orientation Checklist (Manager) and Orientation Checklist (Administrative Staff) are custom designed training programs geared to prepare the individuals for management and administrative staff positions.

The IO may assign new Administrative Staff or Managers to an experienced Administrative Staff or Manager to serve as a preceptor during the orientation period. The preceptor will provide the new Administrative Staff or Manager with guidance in function pertaining to his/her position in compliance with the HRPP Plan.

In addition, Managers and Administrative Staff will complete the web based training modules that are listed in the CITI Training Guidebook. Managers and Administrative Staff will be given a 6 month time period in which they must have completed all of the Initial CITI Modules.

Employees will document the confirmation of their understanding of each of the items in the orientation on the Employee Orientation Form and Individual Training and Education Form or documented by the Internal Communication Exchange (ICE) system.

Periodic Assessment of Skills and Performance

The IIRB, Inc. is dedicated to ensuring that Managers and Administrative Staff have the appropriate training to support the functions of the organization. To fulfill this requirement, the IIRB, Inc. periodically assesses the skills and performance of the each Manager and Administrative Staff individually as well as cumulative part of the organization.

On an annual basis, the CEO and IO or designees will evaluate the following:

- Attendance
- Teamwork
- Knowledge of HRPP Plan, WIs and regulatory requirements
- Completion of continuing education requirements
- Contribution to organization
- Overall performance
- Random quality assurance of assigned projects

Continuing Education

Training is continuous at the IIRB, Inc. at all levels to ensure that oversight of human research is ethically grounded and consistent with current regulatory and policy requirements. The members of the IOAG and IRB may determine when continuing education is warranted for Managers and Administrative Staff. In addition, Administrative Staff can request training sessions of specific topics at any time. Training and education may be offered by in-service trainings at IRB Meetings or Staff Meetings, training workshops, small group roundtable discussion, or review of appropriate publications, updated polices, work instructions, and work forms. In addition new information or quality improvement finding that may affect the HRPP Plan, including laws, regulations, policies, procedures, and emerging ethical and scientific issues will be communicated electronically, or in a staff meeting or training session. Evidence of training will be documented on the Individual Training and Education Form or the Board Training and Education Form or documented by the Internal Communication Exchange (ICE) system. The organization also enrolls in periodic webinars to further provide up to date insight related to human research protection.

The IIRB, Inc. has developed an instant form of communication called Internal Communication Exchange (ICE) system. The purpose of the Internal Communication Exchange (ICE) system is to effectively communicate changes to policies and procedures, updates to forms, and guidance for maintaining the HRPP Plan to staff within the organization prior to a monthly Staff Meeting. An Individual Training and Education Form will be generated in the ICE system and will include a summarization of the continuing education and training activities completed for Manager and Administrative Staff at the IIRB, Inc.

Managers and Administrative Staff are required to complete refresher modules through CITI every 3 years. The organization will also provide support to send Managers and Administrative Staff to attend relevant HRP conferences (e.g., AAHRPP, PRIM&R, NAIM, NIH, or SOCRA).

See Individual Training and Education Form, Board Training and Education Form, Orientation Checklist (IRB Member), Vice Chair in Training Checklist, Orientation Checklist (Manager), and Orientation Checklist (Administrative Staff)

INFORMED CONSENT PROCESS AND DOCUMENTATION PLAN

HRPP PLAN ATTACHMENT 10

PURPOSE

The purpose of the Informed Consent Process and Documentation Plan is to provide guidance for the IRB and Investigators to comply with requirements that Informed consent is sought from each research participant 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.

SCOPE

The Informed Consent Process includes Informed Consent Process elements, and Informed Consent Form elements. The purpose of these elements is to provide guidance to investigators and individuals developing a sample Informed Consent Form, and to provide guidance to investigators of the element the IRB reviews when evaluating a site's informed consent process. These elements are also provided in the Investigator's Guidebook for referencing. The Informed Consent Process and Documentation Plan is also integrated in the Site Evaluation Plan and the Research Evaluation Process and Plan.

INFORMED CONSENT PROCESS

The IRB requires that a Site conducting research has a documented process for obtaining informed consent. The IRB through the Site Evaluation Plan and Research Evaluation Process and Plan makes this determination.

The Principal Investigator is responsible for assuring that the research participant understands his/her rights as a research participant in a research study and what his/her involvement will entail (for example, the risks, benefits and study procedures) and that the research participant gives his/her written consent to participate in the research study prior to the beginning of any study related procedures.

The responsibility for completing and documenting the consent process and reviewing/discussing the study with the research participant and may be delegated to a qualified individual, who has documentation of informed consent training, and has knowledge of the research protocol to answer questions.

The Investigator will document his/her standard operating procedures for the informed consenting process on the Site Questionnaire or by submitting these policies. A Manager will review these procedures and document findings on the Research Evaluation Form. The IRB will review these procedures to determine if they meet the following criteria for approval:

- The investigator or designee will obtain the legally effective informed consent of the research participant or the research participant's legally authorized representative.

- The language is understandable to the subject, based on the research participant's education level and language ability.
- The consent process will be in a private quiet area.
- The research participant or the legally authorized representative will be given sufficient opportunity and privacy to voluntarily consider whether to participate without any influence or coercion
- The research participant will be given the consent form to bring home and discuss with their family.
- The individuals communicating information to the research participant or the legally authorized representative during the consent process will be adequately trained in consenting procedures and will provide the information in language that the research participant or the representative understands well.
- The information being communicated to the research participant or the representative during the consent process specific to will not include any exculpatory language through which the research participant or the legally authorized representative is made to waive or appear to waive any of the research participant's legal rights.
- If a research participant is being enrolled or the legal guardian for the research participant being enrolled cannot adequately read the consent form, procedures must be in place for an impartial witness to be involved in the consent process. Definition of an "impartial" witness is required as a component of the procedures.

The IIRB Inc., reserves the right to observe or have an impartial third party observe the consent process, research and research facility in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that research participants are truly giving informed consent

Such monitoring may be particularly warranted where the research presents significant risks to research participants, studies that involve particularly complicated procedures or interventions, studies involving highly vulnerable populations (e.g., ICU patients, children), studies involving study staff with minimal experience in administering consent to potential study participants, studies that the research participants are likely to have difficulty understanding the information to be provided, or any other situation when the IRB has concerns that consent process is not being conducted appropriately. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

DETERMINATION OF DECISION-MAKING CAPACITY

The decision-making capacity of a potential research participant should be evaluated when there are reasons to believe that the research participant may not be capable of making voluntary and informed decisions about research participation. The investigator and research staff must have adequate procedures in place for assessing and ensuring research participants' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate.

For research protocols that involve research participants with mental disorders that may

affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

Both investigators and IRB members must be aware that for some research participants, their decision-making capacity may fluctuate. For research participants with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process may be necessary.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may research participants be forced or coerced to participate.

In the event research participants become incompetent or impaired in decision-making capacity after enrollment, the PI is responsible for notifying the IIRB, Inc.

DETERMINING CAPACITY TO CONSENT

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

- Ability to evidence a choice,
- Ability to understand relevant information,
- Ability to appreciate the situation and its likely consequences, and
- Ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such research participants on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

The majority of studies conducted at IIRB, Inc. only allow enrolling research participants who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, there must be someone who is able to assess capacity of each potential research participant to consent. The PI may determine after appropriate medical evaluation that the prospective research participant lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. Additionally, if the reason for lack of capacity is because of mental illness then a psychiatrist or licensed psychologist must confirm this judgment and document in the individual's medical record in a signed and dated progress note.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential research participant must then be notified. Should the person object to participating, this objection

should be heeded.

PARTICIPANTS LACKING CAPACITY TO GIVE CONSENT

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained as identified in this Plan. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the research participant's understanding and, if possible, the research participant should give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

Both investigators and IRB members must be aware that for some research participants, their decision-making capacity may fluctuate. For research participants with fluctuating decision-making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may research participants be forced or coerced to participate.

PHYSICIAN-PATIENT RELATIONSHIP

When an Investigator serves as a research participant's primary physician, the IRB will evaluate if additional consideration are necessary to minimize the possibility of undue influence and coercion due to the relationship between the Investigator and the research participant particularly during the informed consent process. The IRB will evaluate if the Investigator has put protections in place, in light of the physician-patient relationship and trust, so that a patient will not be unduly influenced to participate as a research participant in a research study. Such measures could include having someone else conduct the consenting process and study procedures in which the outcome could be influenced due to the relationship. This is particularly true for therapeutic research studies.

NON-ENGLISH SPEAKING RESEARCH PARTICIPANTS

The IIRB, Inc. requires that the language communicated to the research participants is in a language that the participant understands well. For those participants who do not speak English, a qualified and trained individual fluent in the native language of the participant must be available during the informed consent process and duration of the study to answer questions and provide translation. In addition, a person fluent in the translation language must review the approved translated study documents prior to being used to ensure that the translation is consistent with any local dialect.

INFORMED CONSENT FORM

The Organization maintains an informed consent form template that includes suggested

language for compliance with the consent elements required by the FDA as outlined in 21 CFR 50.25, research conducted under DHHS/OHRP Guidelines must meet the requirement in 45 CFR 46, and research under EPA must meet the requirements in 40 CFR Parts 9 and 26, Protections for Research participants in Human Research, and Final Rule. The informed Consent Form will address the elements required by ICH/GCP Guidelines as warranted. Federal, State and local laws will be observed.

The IOAG will review the Informed Consent Form Template on at least an annual basis or as needed. Revisions will be made to the Informed Consent Form Template to accommodate updates to regulations or guidance, request by the IRB, updates to the HRPP Plan, or request and/or feedback of clients.

The Informed Consent Form Template will be used when developing a draft an Informed Consent Form as a service to a client. The Informed Consent Form Template serves as a tool for Informed Consent Form development. All informed consent forms shall contain the basic elements of informed consent form and any of the additional elements of the informed consent form as applicable.

The IIRB, Inc. will utilize a Research Evaluation Form as a guidance tool for these elements and keep the completed form with the study file. All required elements must be included in the consent form unless it is determined that the element is not applicable. The information that is included in the informed consent form can exceed the information provided by the research protocol, if in the IRB's judgment the information is not contradictory to the protocol and is meaningful to the protection of the rights, safety and/or well being of the research participants.

The informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the research participant or the research participant's legally authorized representative at the time of consent.
2. A copy of the signed and dated consent form must be given to the person signing the form.
3. The consent form is a written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the research participant or the research participant's legally authorized representative, but the research participant or representative must be given adequate opportunity to read it before it is signed.
4. The consent form is at a reading level that the research participants can understand well.

When research is "non-therapeutic" in nature, specific justification for the enrollment of research participants that are not able to provide consent on their own behalf is required.

Basic Elements of Informed Consent Form

1. A statement that the **study involves research**, an explanation of the **purposes** of the research and the expected duration of the research participant's participation, a description of the **procedures** to be followed, and identification of any procedures which are experimental; a description of any reasonably foreseeable **risks** or discomforts to the subject;
2. A description of any **benefits** to the research participant or to others which may reasonably be expected from the research;
3. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
4. A statement describing the extent, if any, to which **confidentiality** of records identifying the research participant must be maintained;
5. For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury**, including who will pay for the treatment and whether other financial compensation is available;
6. An explanation of whom to contact on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject;
7. Contact information for the IRB to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the research participant wishes to talk to someone other than the research staff.
8. A statement that participation is **voluntary**, refusal to participate will involve no penalty or loss of benefits to which the research participant is otherwise entitled, and the research participant may discontinue participation at any time without penalty or loss of benefits to which the research participant is otherwise entitled;
9. For **FDA-regulated studies**, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding research participant confidentiality.

Additional elements of informed consent form to be applied, as appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to research participants is not well known.)
2. A statement that if the research participant is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
3. Anticipated circumstances under which the research participant's participation may be terminated by the investigator without regard to the research participant's

consent. (For example: Include when there are anticipated circumstances under which the investigator may terminate participation of a subject.)
4. Any additional costs to the research participant that may result from participation in the research. (For example: Include when it is anticipated that research participants may have additional costs.)
5. The consequences of a subject's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences.
6. Procedures for orderly termination of participation by the subject. (For example: Include when the protocol describes such procedures.)
7. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)
8. The approximate number of research participants involved in the study. (For example: Include when the research involves more than minimal risk.)

ICH-GCP elements of the informed consent form (E6R1)

1. That the trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subject's responsibilities.
6. Those aspects of the trial that are experimental.
7. The reasonably foreseeable risks or inconveniences to the research participant and, when applicable, to an embryo, fetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the research participant should be made aware of this.
9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
10. The compensation and/or treatment available to the research participant in the event of trial-related injury.
11. The anticipated prorated payment, if any, to the research participant for participating in the trial.
12. The anticipated expenses, if any, to the research participant for participating in the trial.
13. That the subject's participation in the trial is voluntary and that the research participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the research participant is otherwise entitled.
14. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the

confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the research participant or the subject's legally acceptable representative is authorizing such access.

15. That records identifying the research participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
16. That the research participant or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
17. The person(s) to contact for further information regarding the trial and the rights of trial research participants, and whom to contact in the event of trial-related injury.
18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
19. The expected duration of the subject's participation in the trial.
20. The approximate number of research participants involved in the trial.
21. The approval of the IRB. (note: the IRB satisfies this element by stamping the approved Informed Consent Form(s) "Approved By Independent IRB").

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the research participant or by the research participant's legally acceptable representative, and by the person who conducted the informed consent discussion.

If a research participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to research participants, is read and explained to the research participant or the research participant's legally acceptable representative, and after the research participant or the research participant's legally acceptable representative has orally consented to the research participant's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the research participant or the research participant's legally acceptable representative, and that informed consent was freely given by the research participant or the research participant's legally acceptable representative.

Except as described below, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in research participants who personally give consent and who sign and date the written informed consent form.

1. Non-therapeutic trials may be conducted in research participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
2. The objectives of the trial can not be met by means of a trial in research participants who can give informed consent personally.
3. The foreseeable risks to the research participants are low.
4. The negative impact on the research participant's well-being is minimized and low.
5. The trial is not prohibited by law.
6. The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such research participants, and the written approval/ favorable opinion covers this aspect.

Informed Consent Form Signature Requirements

Although not required by FDA regulations, the IRB recommends that the time of consent be documented with the signature of the subject. The signature of the Investigator on the consent document is not a requirement by the Organization, however, when the signature line for the Investigator is present, it is intended to affirm that the Investigator takes responsibility for the informed consent process.

For therapeutic studies, if the research participant or the research participant's legally acceptable representative (LAR) cannot read, an impartial witness must be present to read the informed consent form and any other written information supplied to the subject. See Glossary for definition of an impartial witness.

NON-ENGLISH SPEAKING RESEARCH PARTICIPANTS

The Investigational site is required to provide a translated consent (and other documents pertinent to the study) that is/are accurate. Certified translation is required for all Informed Consent Form translations (and other documents pertinent to the study). Spanish Language translations will be reviewed by a member of the IIRB, Inc. for acceptability/accuracy. The certificate of translation for the translated documents is required to include specific reference to the documents that have been translated including specific version and approval dates so as to relate the certificate of translation to the translated document.

A consultant may be utilized for review of non-English information if determined to be necessary by the Chair, Vice Chair, or IRB.

The qualification of the certified translator will be reviewed and either found acceptable or not acceptable.

WAIVER OF INFORMED CONSENT

Research under DHHS

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

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate,

or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not practicably be carried out without the waiver or alteration.

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
(1) The research involves no more than minimal risk to the research participants;
(2) The waiver or alteration will not adversely affect the rights and welfare of the research participants;
(3) The research could not practicably be carried out without the waiver or alteration; and
(4) Whenever appropriate, the research participants will be provided with additional pertinent information after participation.

FDA regulations do not provide for waivers of informed consent except in emergency situations. The IRB does not review research in emergency situation.

<u>Research under EPA</u>
The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
(1) The research or demonstration project is to be conducted by or subject to the approval of State or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not practicably be carried out without the waiver or alteration.

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
(1) The research involves no more than minimal risk to the research participants;
(2) The waiver or alteration will not adversely affect the rights and welfare of the research participants;
(3) The research could not practicably be carried out without the waiver or alteration; and
(4) Whenever appropriate, the research participants will be provided with additional pertinent information after participation.

WAIVER OF INFORMED CONSENT FORM

Research under DHHS

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

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

(2) That the research presents no more than minimal risk of harm to research participants and involves no procedures for which written consent is normally required outside of the research context.

Research under EPA

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

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

(2) That the research presents no more than minimal risk of harm to research participants and involves no procedures for which written consent is normally required outside of the research context.

Research under FDA

The IRB shall require documentation of informed consent in accordance with 21 CFR 50.27, except as follows:

(1) The IRB may, for some or all research participants, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to research participants and involves no procedures for which written consent is normally required outside the research context;

When the documentation requirement is waived under FDA, DHHS, or EPA regulations as previously listed, the IRB may require the investigator to provide research participants with a written statement regarding the research.

The IRB can also alter the requirements of documented informed consent based on the Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable dated 4/25/2006.

The FDA believes that it is possible in certain circumstances for IVD device investigations to be conducted using leftover specimens obtained without informed consent while protecting the human research participants who are the source of such specimens.

The IRB has the authority to allow these leftover specimens to be obtained without informed consent under the circumstances that the research involves the use of unlinked and de-identified remnant samples collected through the normal course of patient care. Documentation must be provided addressing the mechanisms for assuring confidentiality.

The FDA intends to exercise enforcement discretion as to informed consent requirements for clinical investigators, sponsors, and IRBs if an *in vitro* diagnostic device investigation is performed and all of the following are true:

a) The investigation meets the IDE exemption criteria at 21 CFR 812.2(c) (3)
b) The study uses leftover specimens, that is, remnants of specimens collected for routine clinical care or analysis that would have been discarded. The study may also use specimens obtained from specimen repositories or leftover specimens that were previously collected for other research purposes.
c) The specimens are not individually identifiable, i.e., the identity of the research participant is not known to and may not readily be ascertained by the investigator or any other individuals associated with the investigation, including the sponsor. If the specimen is coded, it will be considered to be not individually identifiable if neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the research participant from whom the specimen was collected, either directly or indirectly through coding systems.
d) The specimens may be accompanied by clinical information as long as this information does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor.
e) The individuals caring for the patients are different from and do not share information about the patient with those conducting the investigation.
f) The specimens are provided to the investigator(s) without identifiers and the supplier of the specimens has established policies and procedures to prevent the release of personal information.
g) The study has been reviewed by an IRB in accordance with 21 CFR Part 56, except as described in section 7 of this guidance document.

GENERIC INFORMED CONSENT FORMS

The IIRB, Inc. will review submitted generic informed consent forms that are not directly related to a specific research study including but not limited to the following:

- Site HIV Informed Consent Form
- HIPAA Authorization Form
- Pre-Screening Forms

These generic consent forms will be reviewed to ensure that the basic element of consent including the extent to which confidentiality of the data will be protected. This review can be performed under expedited review procedures or reviewed by the

convened IRB. At the time of the review, the reviewers may grant favorable opinion for use in clinical research and an approval period will be granted which may exceed 12 months. Use of generic ICFs that are addressed in the research protocol need to be reviewed by the IRB. If a generic ICF is not addressed in the research study and is not an investigational aspect of the research, review by the IRB is not warranted.

HIPAA WAIVER
The IRB is authorized to conduct HIPAA Waiver reviews.

USE OF SHORT FORM OF CONSENT DOCUMENTATION
The IRB does not allow the use of short form of consent documentation.

See attached IIRB, Inc. Informed Consent Form Template

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

RESEARCH PARTICIPANT OUTREACH PROGRAM PLAN

HRPP PLAN ATTACHMENT 11

PURPOSE

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 the effectiveness to ensure that educational opportunities are offered to research participants, prospective research participants, and community members that will enhance their understanding of research involving human participants in research conducted under its oversight.

SCOPE

The Research Participant Outreach Program is intended to reach both individuals that have committed to participation in a research study and to those that may be interested in finding out more about research and their role and rights as a research participant.

RESPONSIBILITY

The Participant Outreach Program Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

PROGRAM COMPONENTS

1. All Informed Consent Forms include an explanation of whom to contact on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject;
2. All Informed Consent Forms include contact information for the IRB Chair or designee and the IIRB, Inc. to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff.
3. All Informed Consent Forms include contact information for the IIRB, Inc. website. The IIRB Inc., dedicates a section of the website to individuals that may be interested in learning about research and their role and rights as a research participant. This portion of the website is titled "Research Participants". This website includes resources, such as the role of IIRB, Inc., questions to ask before and after a subject decides to participate in a research study, key research terms, additional resources with their relative links, and contact information.
4. IIRB, Inc. makes available to all of its sites conducting human research a "Research Participant Brochure" that provides subjects with information on research, their rights as a research participant, and contact information.
5. IIRB, Inc. provides several relevant links to the Food and Drug Administration, Office for Human Research Protections (OHRP), and other regulatory agencies

to inform the general public about research participation. Participants, prospective participants, and community members may access this information from the "Research Participants" section of the IIRB, Inc website to increase public awareness and educate potential research participants.

6. IIRB, Inc. provides training to investigators and key research staff conducting human research studies through power point presentations, and through CITI training modules offered through the IIRB, Inc.
7. The IIRB, Inc. will partner with research sites to conduct "Subject Satisfaction" surveys that include HRP elements

These activities are reviewed on an annual basis as a component of the review of the HRRP Plan. Consideration of changes will be made and include evaluation outcomes and feedback from Sites and Research Participants.

See Attached Research Participant Brochure and Research Participant Website Overview

VULNERABLE POPULATION PROTECTION PLAN

HRPP PLAN ATTACHMENT 12

PURPOSE

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 research participants, to ensure the site has 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.

SCOPE

The Vulnerable Populations Plan includes mechanisms for identifying vulnerable populations being enrolled as research participants, and providing additional safeguards to protect these populations. The plan includes regulatory requirements for identifying and enrolling these populations, and additional areas of concern to consider when reviewing a research study involving such populations.

RESPONSIBILITY

It is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

DEFINITION

Vulnerable research participants include children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged person.

MECHANISMS

The review process of a research study and research site integrates the information provided by the Investigator by means of the site questionnaire, research protocol, and supporting documentation. This information is compiled, analyzed, and documented in the research evaluation portion and board evaluation portion of the Research Evaluation Form. Specific findings and direction may be identified and communicated to the Principal Investigator through the approval letter.

RESEARCH INVOLVING CHILDREN

The following applies to all non-EPA research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children. Definitions related to research involving children can be located in the HRPP Plan Glossary.

Federal regulations (45 CFR 46.402/21 CFR 50.3) define children as persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the

research will be conducted. In addition to specifying an age of majority, most states allow minors to consent for themselves for certain medical treatments. Therefore, minors who can legally consent to the treatment or procedures involved in the research are not considered "children". IIRB, Inc. places the responsibility for determining whether children are involved in research with the investigator. Investigators will be required to provide a determination for involving children in their research and the basis for how they arrived at that determination. The IRB will evaluate the adequacy of the investigator's determination. IIRB, Inc. legal counsel may be consulted for applicable laws of the jurisdiction in which the research will be conducted. Pediatric research participants represent a vulnerable population, therefore, special attention is needed to protect their rights and shield them from undue risk.

EPA Guidelines prohibit research that is conducted or supported by the EPA or intended to be submitted to the EPA from involving intentional exposure of human research participants who are children. Consideration of enrollment of children in observational studies (any study that does not meet the criteria for intentional exposure) can be approved and must meet all other IRB and EPA requirements, including determination of the need for Assent by the child.

Adequate provisions for soliciting the consent of the parent(s)/legal guardian and assent of the children is necessary as listed in the Informed Consent Form Process and Documentation Plan (Attachment 10).

PROCEDURE

When the IRB reviews research involving children, the Board portion of the Research Evaluation Form will include questions that support this policy and procedure, and guide the IRB in making a determination as to which category for approval the study meets. The IRB Chair or Vice Chair will lead the IRB through the questions pertaining to the category of approval for research involving children and the IRB determinations will be documented in the IRB Meeting Minutes.

ASSESSMENT FOR APPROVAL

The IRB will determine one of the following criteria and document each starred finding and protocol-specific findings justifying each determination:

1. 50.51
    a. The clinical investigation involves not greater than minimal risk to the research participants;* and
    b. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as listed below.
2. 50.52
    a. The clinical investigation involves greater than minimal risk but presents the prospect of direct benefit to individual research participants;*
    b. The risk is justified by the anticipated benefit to the research participants;*
    c. The relation of the anticipated benefit to the risk is at least as favorable to the research participants as that presented by available alternative approaches;* and

d. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as listed below.

3. 50.53
   a. The clinical investigation involves greater than minimal risk and no prospect of direct benefit to individual research participants, but is likely to yield generalizable knowledge about the research participants' disorder or condition;* :
   b. The risk represents a minor increase over minimal risk;*
   c. The intervention or procedure presents experiences to research participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;*
   d. The intervention or procedure is likely to yield generalizable knowledge about the research participants' disorder or condition that is of vital importance for the understanding or amelioration of the research participants' disorder or condition;* and
   e. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as listed below.
4. 50.54
   a. The clinical investigation is not otherwise approvable (does not meet 50.51, 50.52, or 50.53) but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children;*
   b. The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;* and
   c. The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:
      i. That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or
      ii. That the following conditions are met:
         1. The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
         2. The clinical investigation will be conducted in accordance with sound ethical principles; and
         3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as listed below.

If the research is conducted or supported by the EPA or intended to be submitted to the EPA the IRB will determine and document that the research does not involve intentional exposure of human research participants who are children.

ADEQUATE PROVISIONS FOR SOLICITING THE PERMISSION OF PARENTS OR GUARDIANS

The IRB will determine and document which of the following provisions for permission of parents and guardians will be followed:

1. The permission of both parents is required if both parents are alive, known, competent, reasonably available, and have legal responsibility for the care and custody of the child. Otherwise the permission of one parent is required; OR

2. The permission of one parent is sufficient, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. (Not allowed for Categories 50.3 and 50.4.)

ADEQUATE PROVISIONS FOR SOLICITING THE ASSENT OF CHILDREN

1. The IRB will determine and document whether assent is a requirement of:
    a. All children.
    b. Some children.
    c. None of the children.
2. When the IRB determines that assent is not a requirement of some children, the IRB will determine and document:
    a. Which children are not required to assent.
    b. Which justification is being used to waive consent:
    c. The children are not capable of providing assent based on the age, maturity, or psychological state.
    d. The capability of the children is so limited that they could not reasonably be consulted.
    e. The intervention or procedure involved in the research holds out a prospect of direct benefit that was important to the health or well being of the children and is available only in the context of the research.
    f. The assent can be waived using the following criteria:
        i. The clinical investigation involves no more than minimal risk to the research participants;
        ii. The waiver will not adversely affect the rights and welfare of the research participants;
        iii. The clinical investigation could not practicably be carried out without the waiver; and
        iv. Whenever appropriate, the research participants will be provided with additional pertinent information after participation.
3. When the IRB determines that assent is a requirement, the IRB will determine and document whether assent will be documented.
4. When the IRB determines that assent is a requirement and will be documented, the IRB will determine and document the process to document assent.

PREGNANT WOMEN AND FETUSES

The IRB does not routinely review research studies that focus on pregnant women or fetuses as research participants or involves intentional exposure of human research participants who are pregnant women unless the purpose of the research was to meet the health needs of the mother with minimal risk to the fetus.

For research not funded by DHHS, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research where the risk to the fetus is no more than minimal.

In research involving pregnant women not funded by DHHS involving more than minimal risk to fetuses, the IRB will review the research protocol and Investigator's Brochure/Product Information to determine that the following conditions are met prior to approval:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

In research involving pregnant women funded by DHHS, 45 CFR Subpart B applies to all research involving pregnant women. The IRB will review the research protocol and Investigator's Brochure/Product Information to determine that the following conditions

are met prior to approval:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
(c) Any risk is the least possible for achieving the objectives of the research;
(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions;
(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
(g) For children who are pregnant, assent and permission are obtained in accord with the provisions related to research involving children;
(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

Additional considerations will be given to evaluate opportunities in the research design to improve the risk/benefit ratio for both the mother and fetus.

In research involving women of childbearing potential, although it is not intended that the research participant will become pregnant during participation, it is a possibility and is therefore evaluated by the IRB. In this situation, the IRB evaluates the appropriateness of contraception and pregnancy testing during the study as well as information related to mutagenic and teratologic tendencies from available clinical and nonclinical data. In addition, precautions and potential risk of becoming pregnant will be identified in the informed consent form.

EPA Guidelines prohibit research that is conducted or supported by the EPA or intended to be submitted to the EPA from involving intentional exposure of human research participants who are nursing women, or pregnant women.

MENTALLY IMPAIRED PARTICIPANTS

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

1. Only incompetent persons or persons with impaired decision making capacity are suitable as research participants. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as research participants. Incompetent persons or persons with impaired decision-making capacity must not be research participants in research simply because they are readily available.

2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be research participants of research that imposes a risk of injury, unless that research is intended to benefit that research participant and the probability of benefit is greater than the probability of harm.

3. Procedures have been devised to ensure that participant's legally authorized representatives (LARs) are well informed regarding their roles and obligations to protect incompetent research participants or persons with impaired decision making capacity. LARs must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the research participant would do if competent, or if the research participant's wishes cannot be determined, what they think is in the incompetent person's best interest.

The decision-making capacity, determining capacity to give consent, and requirements for consent and assent will be assessed as outlined in the Informed Consent Process and Documentation Plan.

OTHER VULNERBALE POPULATIONS

The IRB does not review research studies that involve the following vulnerable populations as research participants.

1) Prisoners
   a) In the event the IRB receives notification that a research participant has become imprisoned, IIRB, Inc. policy requires that the research participant be withdrawn from the study, or the study be referred to an IRB that reviews studies with prisoners as research participants and has a prisoner representative.

2) Wards
   a) In the event the IRB receives notification that a research child has become a ward of the state, IIRB, Inc. policy requires that the child be withdrawn from the study, or the study be referred to an IRB that reviews studies with child as wards and has a ward of the state representative.
3) Neonates (viable and nonviable)
4) After delivery materials such as the placenta, the dead fetus or fetal material.

POTENTIALLY VULNERABLE POPULATIONS

The Research Evaluation Process will review and identify potentially vulnerable research participants such as disabled (handicapped), mentally disabled persons, economically disadvantaged persons, educationally disadvantaged persons and others not otherwise described in the federal regulations. The IRB will implement protective measures as appropriate based on specific population and the nature of protocol.

PURPOSE

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.

SCOPE

Relevant study documents will be distributed to all members scheduled for an IRB meeting so that sufficient time is given to review the documents prior to the meeting. Generally all materials are provided to the members 4 days prior to the scheduled meeting. A tentative meeting agenda and prior minutes will be prepared by a Manager and distributed to the IRB members prior to commencement of a convened IRB meeting. Any IRB member may request any additional materials submitted for review by contacting the IIRB, Inc.

IRB Members (including alternate members) will receive all relevant study documents for each IRB Meeting in which they are scheduled. All IRB members (including alternates) scheduled for an IRB Meeting are provided and are expected to review the materials listed below in advance of the meeting to be familiar with them and able to discuss them at the IRB meeting.

Each of the items listed below will also be reviewed in depth by one or more IRB Members to be able to provide information to the convened IRB to support the collective discussion in determining the criteria for approval. The documents to be reviewed in depth are not required to be reviewed by the same IRB member and may be reviewed by multiple IRB members as long as documents are reviewed and the reviewing IRB members will be present at the scheduled meeting. The following outlines the distribution of documents.

Type of review	**All IRB Members are provided and are expected to review these materials in advance of the IRB meeting**
Initial	▪ Draft Informed Consent Form (as applicable) ▪ Site Questionnaire (as applicable) ▪ Recruitment materials (as applicable) ▪ The full protocol ▪ The following information, if not in the sponsor protocol: o A description of procedures already being performed for diagnostic or treatment purposes. o When some or all of the participants were likely to be vulnerable, a description of additional safeguards included in the protocol to protect their rights and welfare. ▪ Any relevant grant applications. ▪ The investigator's brochure or Product Information (when one existed)(must be reviewed by a scientific member). ▪ The DHHS-approved sample informed consent document (when

	one exists). ▪ The complete DHHS-approved protocol (when one exists).
Continuing Review	▪ Site Questionnaire (as applicable) ▪ The full protocol. ▪ The following information, if not in the sponsor protocol: o A description of procedures already being performed for diagnostic or treatment purposes. o When some or all of the participants were likely to be vulnerable, a description of additional safeguards included in the protocol to protect their rights and welfare. ▪ The Continuing Review Report, Progress Report Form as applicable. ▪ The investigator's brochure or Product Information (when one existed)(must be reviewed by a scientific member). ▪ The IIRB, Inc. approved current informed consent form. ▪ Any newly proposed informed consent form.
Modifications involving addition of a new site	▪ Site Questionnaire and supporting documents.
All other modifications	▪ Submission of modification and supporting documents as relevant.

DISTRIBUTION METHODS

Submissions that require approval and do not meet the criteria for expedited review for initial review or continuing review, or modifications to ongoing research, or problems in research will be provided to IRB members scheduled for an upcoming IRB Meeting. If documents are unable to be published using the BizSuite system, hard copies will be provided to the IRB Members prior to the scheduled IRB Meeting.

RESPONSIBILITY

This Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

INTERNATIONAL RESEARCH EVALUATION PLAN

HRPP PLAN ATTACHMENT 14

PURPOSE

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

SCOPE

The IIRB, Inc. is committed to ensuring that research conducted at international sites meets the same level of protection for human research participants as research conducted within the U.S. sites. The criteria listed in this International Research Evaluation Plan will be used to evaluate the medical and site qualifications and IRB/IEC requirements for specific countries. The IIRB, Inc. does not review research conducted in Canada, and generally limits its oversight to Latin American and Caribbean locations. The IIRB, Inc. at the discretion of the IO may review and approve other research for compliance with FDA/DHHS and ICH regulations, however the site is notified that local regulatory review or community standards as applicable are required. This plan is in addition to the elements listed in the Research Evaluation Plan and Site Evaluation Plan.

PROCESSES

The International Addendum to the Site Questionnaire is the primary tool for documenting international compliance in research studies. The IRB obtains medical license/ or equivalent (i.e. Registration #) confirmation and CV documentation of qualifications consistent with processes in the U.S. and ICH-GCP guidelines. The IRB reviews and evaluates the qualifications of the investigator as outlined in the Site Evaluation Plan.

The IRB relies on the signed Site Questionnaire as validating information. In addition to the verification conducted by the IRB through continuing due diligence, ICH-GCP requires the Sponsor to select qualified investigators and to submit any required application to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial (5.10).

The following additional processes support compliance:

- The IIRB, Inc. will conduct periodic site visits to Latin America and the Caribbean to assess cultural mores, site qualifications and facilities.
- The IIRB, Inc. will assess the site management support in the U.S. (evaluation of qualification of CRO and requirement for local U.S. contact).
- The IIRB, Inc. maintains an ongoing relationship with consultants who have knowledge and experience in Latin American and Caribbean regulatory requirements.

APPLICABLE REGULATORY REQUIREMENTS

Focus of regulatory support for these processes are oriented towards the following ICH-

GCP guidelines due to the nature of the site selection process. The FDA/DHHS regulatory requirements are consistent with research conducted in the U.S.

ICH-GCP 3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

ICH-GCP 5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

ICH-GCP 5.10 Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

EVALUATION OF MEDICAL QUALIFICATIONS

The IRB ensures that the Principal Investigator and/or Sub-Investigator(s)for international research have been registered with the Ministry of Health or its equivalent institution in their respective country and maintains his/her registration number or equivalent in good standing. The PI and/or Sub-Investigator(s) shall provide accurate documentation of such status. The IRB evaluates the qualifications of the investigator and the site utilizing the Site Questionnaire and through a review of the submitted CV/license or equivalent (i.e. Registration #). The IRB will consider the qualifications of the investigator for the proposed trial, as documented by current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests (ICH- GCP 3.1.3).

The following is an overview of the credentialing process that is generally followed in most Latin American countries (i.e. Honduras, Dominican Republic, Ecuador, Panama, Costa Rica) for credentialing a physician to practice medicine in the respective country. For purposes of this document, the physician will be referred as the investigator:

The investigator presents documentation of their undergraduate work, medical school training and/or specialization (i.e. Internship, Residency, and/or fellowship or equivalent country-specific term), along with any other requested item to the Ministry of Health or its equivalent country-specific institution. The Ministry of Health or authorized delegate (i.e. credentialing panel/committee) will review the documentation provided and ensure its accuracy and validity. Upon review and approval, the requesting investigator is given a registration number which authorizes him/her to be able to practice medicine in that particular country. Please note that this may not include additional legal requirements necessary for establishing a medical practice in the respective country as a business.

In contrast to the re-credentialing process practiced in the United States (i.e. every 2 or 4 years with the required CEUs and renewed medical license), physicians are expected to ensure ongoing continuing education in the medical field as part of their professional responsibility. It should be noted that country residents have the right to file a physician complaint with the Ministry of Public Health or equivalent institution. Thus, restrictions and/or suspensions can be issued to the physician resulting in their registration number being suspended and/or revoked.

In addition, international Principal Investigators must still meet the requirements listed in the HRPP Plan for Human Research Protection Training.

COUNTRY SPECIFIC IRB/IEC REQUIREMENTS

In addition, to the information provided by the Site/CRO on the Site Questionnaire the following outlines the ethical oversight the IRB uses in its evaluation of IRB/IEC requirements. Due to the increase of clinical trials being conducted in Latin America, many countries are in the process of reviewing their laws in the area of research which includes the protection of human rights. Thus, the following should be considered as a guidance document and not a finalized country requirement document.

Country	Country Requirement
Honduras	None at this time
Ecuador	Approval from the Ministry of Public Health
Dominican Republic	Hospital Based Only
Costa Rica	Informing Ministry of Public Health of Research (CEC-UCIMED must approve the ICF given to the subjects).
Panama	None, *although laws may be changing due to recent legislation*
Brazil	IEC only
Argentina	IEC only
Belize	None at this time

Additional Mechanisms for Protection of International Research Participants

- Focused attention is given to provide toll free access to the IIRB, Inc. for questions, concerns, or complaints a research participant may have.
- Bilingual staff at IIRB, Inc. is accessible to assure adequate communication.
- Spanish translation of Research Participant webpage at www.iirb.com.

RESPONSIBILITY

This Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. In addition, as individual country laws change or different requirements become apparent, the IO may update the document. Prior to changes by the IO, these changes will be evaluated by the IOAG and IRB.

PURPOSE
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.

SCOPE
This disaster plan includes definitions of natural disasters, procedures taken to prepare for such events, and contingency plans for the security of data, communication mechanisms, and measures for the continuity of service. The development of this plan includes the consideration of neighboring businesses and building owners to avoid confusion.

RESPONSIBILITY
The Disaster Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG.

The President and/or CEO serve as the company spokesperson in an emergency.

DEFINITION
Hurricane: a tropical storm with winds of 75 miles per hour or greater. A tropical storm is a cyclonic storm having winds ranging from approximately 30 to 75 miles per hour.

Tornado: a localized, violently destructive windstorm occurring over land, and characterized by a long, funnel-shaped cloud extending toward the ground and made visible by condensation and debris.

Flood: a great flowing or overflowing of water, especially over land not usually submerged.

Fire: a state, process, or instance of combustion in which fuel or other material is ignited and combined with oxygen, giving off light, heat, and flame.

PREPARATION FOR DISASTER
The Chief Operating Officer or designee will verify availability of the following supplies on at least an annual basis and verified that all of the supplies are available at the beginning of Hurricane Season (June 1).

- 5 flashlights
- 5 gallons of water
- 10 gallons of gasoline for generator
- Transistor radio with working batteries
- Backup batteries
- 3 large tarps
- 20 large plastic garbage bags

Fire protection is provided by an overhead sprinkler system and individual wall units are located throughout the facility. These systems are inspected by the City of Plantation Fire Department on at least an annual basis.

Notification of Disaster Forthcoming (48-72 hours)

- Implement hurricane monitoring and tracking through National Hurricane Center, tornado/flood watch through National Weather Center, or Fire through National Emergency Services.
- Staff to notify clients that only necessary review will be conducted.
- All available personnel to report to the office. All pending work is to be completed and distributed.
- Back up data (x2) and remove tape from Site. The Chief Operating Officer or designee and IT contracted personnel are responsible for protecting the data back up.

Disaster Forthcoming (within 24 hours)

- Remove server and appropriate computer equipment from site. Server to remain with the CEO or appropriate designee, some equipment to remain with CEO or appropriate designee in Broward County, some equipment to be stored off site in West Palm Beach or in Miami-Dade County based on anticipated trajectory of the storm.
- Ensure all regulatory documents (i.e., HRPP Plan), minutes, and reference material are in a plastic bag and place in the most “inner” room of the building, and covered with tarp.
- Place pending work in plastic bag, CEO or appropriate designee to maintain work off site in a secure location.
- Secure and cover remaining electronic equipment with a tarp.

Disaster Over

The President and CEO or appropriate designee will assess the facility to determine if the facility is safe to return, and when employees are expected to return.

- Assess facility do determine if the building is safe to return and the security of documents and systems.
- All staff to report and assist with computer re-installation.
- If the facility is damaged, evaluate alternative facilities in which the continuity of service may take place.

CONTINUITY OF SERVICE

In the event that the President and CEO determined that the facility is unsafe or impractical to return, the President and CEO will determine an off-site secure location in order to provide continuity of services. The IT will be notified immediately, and the server, computers, and computer equipment will be relocated to the secure location. Laptops will be the first computers to be moved.

The Chief Operating Officer will ensure that there are sufficient office supplies (i.e., paper, pens, printers, scanners, faxes, etc.) at the secure location. The Chief Operating Officer will also secure the office building, and will either have all calls transferred to the remote location, or place a message on the call system notifying clients of alternate contact information, as applicable.

SECURITY OF DATA

To protect the computer hardware, the computers will be unplugged, removed from windows, covered with plastic or tarps, and stored off the floor in the most inner room of the building. The President and/or CEO may determine that some or all of the hardware is removed from the facility and stored off site.

To protect the computer software, at least 2 backup tapes of the data stored on the server will be made and stored off-site. The President and/or CEO may determine that the server be removed from the facility and stored off-site.

If the computers are destroyed, back-up computers will be used at a convenient alternate location.

COMMUNICATIONS

The IIRB, Inc. will communicate the Disaster Plan with the employees on an annual basis or as updates are warranted. If changes are made to the Disaster Plan the staff will be notified by the Internal Communication Exchange (ICE), Staff Meeting, or other in-service trainings.

The Chief Operating Officer or designee will notify the staff of an upcoming disaster (if applicable) and direct the staff in implementing this plan. When time permits, the Chief Operating Officer will permit employees to personally prepare for the upcoming disaster (i.e., grocery store, prepare home, etc.).

After the disaster is over, members of the Institutional Official Advisory Group (IOAG) will receive direction from the President and CEO on plans to return to the IIRB, Inc. office. Decision to return the office will be based on current status of the disaster, upcoming weather report/advisories and conditions while commuting to the office (i.e., down power lines, no electric, blocked roads). The IOAG members will be assigned specific employees to contact for assessment of staff safety and to notify them when they can return to the facility or an alternate location for the continuity of service. All employees are expected to return when deemed appropriate by the President and CEO. Case by case exceptions can be made is appropriate.

EMPLOYEE EMERGENCY CONTACT INFORMATION

The IIRB, Inc. will maintain a Phone Tree of all employees which includes contact information and an emergency contact. The Phone Tree will be updated on an annual basis or as updates are warranted and distributed to all employees. The Chief Operating Officer will make sure that all members of the IOAG have a current Phone Tree so that staff may be contacted appropriately prior to leaving the facility.

PURPOSE
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).

SCOPE
The Data Security Plan includes mechanism for identifying the systems used at the IIRB, Inc., who has access to the information contained in these systems, who has the authority to revise these systems and the information contained in them, what security measures are in place to ensure the confidentiality of data.

RESPONSIBILITY
The Data Security Plan is approved by the Board of Directors on an annual basis with interim changes initiated by the IO on an as needed basis. Prior to changes by the IO, these changes will be evaluated by the IOAG.

EMAIL SYSTEM
The IIRB, Inc. email is outsourced to Intermedia which provides email hosting and requires an exchange client. The Exchange client uses Microsoft Outlook to pull emails. Outlook will retrieve the emails from the provider to each end user workstation or any configured client.. A Webmail interface is available if the individual decides to access their mail from the internet. Currently the organization uses Microsoft Outlook 2007 to access emails. All employees at IIRB, Inc. use one of these systems to pull emails through the use of Microsoft Outlook Utility. Employees can only access their established email account as the contracted IT establishes and maintains separate accounts for each user.

To maintain security of emails received, stored, and transmitted in the system, all emails are stored locally at the end users system and on the Exchange server. Emails may be archived locally at each end user's computer if desired. These systems require log in by that individual in order to access the emails..

The IIRB, Inc. uses McAfee Security Center (Version 10) for SPAM and Virus protection.

All systems are backed up and archived by the outsourced provider. The password criteria is maintained in a file and may differ depending on when the account was established based on a protocol. IT maintains this file.

CLOSED NETWORK
The IIRB, Inc. has a closed network internal with no outside access. A CD with the passwords is archived outside of the office in a secure location.

The IIRB, Inc. implements security at group levels and these levels are allowed to access certain locations within our network based on a criteria established. We currently

have Manager, Admin. and User groups. Groups may be allowed to access certain parts of the network based on who is in the Groups.

IRB BIZSUITE DATABASE SYSTEM

The IIRB, Inc. has developed an innovative database system in order to fulfill the requirements listed in the Human Research Protection Program Plan (HRPP Plan). This database system is identified as Bizsuite (Version 2.0) and includes modules to assist the Institutional Review Board in their functions, Customer Relationship Management (CRM), organizational planning, financial services, and administration tasks. The current database server is MS SQL Server 2005.

To ensure confidentiality and maintain security of the system, the application security is based on Application Users & Roles, the user password is encrypted using MD5 algorithm, the users rights are limited to the users roles specifically identified for each user, and the database connection is made using a MS SQL Server user with limited access (data read/write to the application's database).

The system program is updated on at least an annual basis with monthly revisions applied as applicable. The system programmer and the administrator of the system has access to make changes to the system. Change to information in the database itself can be revised by internal employees based on their role in the organization.

To protect the system against hackers, viruses, and other potentially hazardous elements the system was tested against SQL injections, periodically all the computers are fully scanned against viruses, and a live antivirus program is installed on each computer in which the database system will be used. In addition, after each major release of updates, a full set of security tests are applied including SQL injection, wrong users, wrong passwords (clarify), and rights for weak users to ensure that the system is in compliance with this plan.

The IRB business data is stored to the database, only IT administrators (consulting companies) has rights to access the database. In addition, a nightly back up of the information stored in the database is performed and the tape is stored at an off-site location.

WEBSITE

The IIRB, Inc. uses XO Communications for a website hosting. The website is updated 2-3 times per year. IT administrators (consulting companies) are the only individuals authorized to make changes to the website. To protect the website against hackers, viruses, and other hazardous elements the information is scanned with anti-virus programs each time an update is made.

To maintain overall security of the website, the IIRB, Inc. has limited administrator access, and the website is protected using the hoster features.