

INVESTIGATOR HANDBOOK

Sterling Institutional Review Board
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Chapter 1 – INTRODUCTION

Sterling Institutional Review Board (IRB) was established in 1991 as an independent ethical review board, whose purpose is to protect the rights and welfare of human subjects who participate in research. While the Principal Investigator is responsible for the conduct of the study, the IRB is responsible for determining that the proposed research is scientifically valid and that the anticipated benefits to the subjects as well as the knowledge that is expected to be gained outweigh the risks.

Sterling IRB operates in compliance with:

- Protection of Human Subjects (DHHS), 45 CFR 46
- FDA Regulations on Human Subjects Research, 21 CFR 50, 56, 312, 812
- Standards for Privacy of Individually Identifiable Health Information, 45 CFR 160, 164
- International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6)

The IRB reviews and monitors research involving human subjects. It has the authority to approve, require modification in (to secure approval), or disapprove research. The purpose of the IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. To accomplish this purpose, the IRB typically uses a group process to review research protocols and related materials. The IRB is responsible for approving what constitutes an adequate informed consent confirming that all necessary elements of informed consent are included. It also reviews the credentials and medical licenses of potential Principal Investigators. Sterling IRB has a policy of continuing education for both the Board members and Administrative Staff to ensure appropriate training in human research subject protections.

If you have any questions or concerns about the responsibilities of the Principal Investigator, please contact the Sponsor/CRO or call us during normal business hours. For questions, comments, or suggestions regarding the review of research at Sterling IRB, please contact us during normal business hours. You may reach us at (770) 690-9491, toll-free at 1 (888) 636-1062, between the hours of 8:30am – 5:30pm, Monday through Friday. Please also visit the Sterling IRB website at <www.sterlingirb.com> for forms, additional information, and links to other sites that will increase your knowledge and understanding of the research process. The IRB is available as a resource to assist investigative sites in any matters that involve research participants (e.g., complaints, concerns).

This handbook outlines the responsibilities of the Principal Investigator and should be read by the key personnel on the research team. We look forward to working with you to ensure the safeguarding of the rights, privacy and welfare of those who volunteer to participate in research studies.

Sterling IRB Mission Statement:

The mission of Sterling Institutional Review Board is to protect the rights, privacy, and welfare of human subjects who volunteer to participate in research studies.

Chapter 2 – THE BELMONT REPORT (Ethical Principles and Guidelines for the Protection of Human Subjects of Research):

The Belmont Report is the cornerstone statement of the ethical principles upon which the Federal Regulations for protection of human subjects are based. Sterling IRB recommends that all Principal Investigators and key research personnel read the introductory guidance below and the Belmont Report.

The following is taken from the OHRP IRB Guidebook.
http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation were begun, sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.

Respect for persons involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.

Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.

Justice requires that the benefits and burdens of research be distributed fairly.

The Report also describes how these principles apply to the conduct of research. Specifically, the principle of *respect for persons* underlies the need to obtain informed consent; the principle of *beneficence* underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of *justice* requires that subjects be fairly selected. As was mandated by the congressional charge to the Commission, the Report also provides a distinction between "practice" and "research." The text of the *Belmont Report* is thus divided into two sections: (1) boundaries between practice and research; and (2) basic ethical principles. The full text of the *Belmont Report*, which describes each of the three principles and its application, is provided in the Guidebook in Appendix 6; a summary follows.

Boundaries Between Practice and Research

While recognizing that the distinction between research and therapy is often blurred, *practice* is described as "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals." The Commission distinguishes *research* as designat[ing] an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. "The Report recognizes that "experimental" procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such "experimental" procedures should be investigated early, and that institutional oversight mechanisms, such as medical practice committees, can ensure that this need is met by requiring that "major innovation[s] be incorporated into a formal research project."

Applying the Ethical Principles

Respect for Persons:

Required by the moral principle of respect for persons (*see* definition, above), **informed consent** contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether to participate, including the research procedure(s), their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw from the research at any time. Responding to the question of what constitutes adequate information, the Report suggests that a "reasonable volunteer" standard be used: "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation." Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. [See discussions on this issue in other sections of the Guidebook, including Chapter 6, "Special Classes of Subjects."] Each such class of persons should be considered on its own terms (*e.g.*, minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for persons requires that the permission of third persons also be given in order to further protect them from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

Beneficence:

Closely related to the principle of beneficence (*see* definition, above), **risk/benefit assessments** "are concerned with the probabilities and magnitudes of possible harms and anticipated benefits." The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and the IRB's insistence upon precise answers to direct questions. The IRB should: (1) determine the "validity of the presuppositions of the research;" (2) distinguish the "nature, probability and magnitude of risk...with as much clarity as possible;" and (3) "determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies."

Five basic principles or rules apply when making the risk/benefit assessment: (1) "brutal or inhumane treatment of human subjects is never morally justified;" (2) risks should be minimized, including the avoidance of using human subjects if at all possible; (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving "significant risk of serious impairment" (*e.g.*, direct benefit to the subject or "manifest voluntariness of the participation"); (4) the appropriateness of involving vulnerable

populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

Justice:

The principle of justice mandates that the **selection of research subjects** must be the result of fair selection procedures and must also result in fair selection outcomes. The "justness" of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (*e.g.*, involving "undesirable" persons in risky research). Further, "social justice" indicates an "order of preference in the selection of classes of subjects (*e.g.*, adults before children) and that some classes of potential subjects (*e.g.*, the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Investigators, institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that "arises from social, racial, sexual, and cultural biases institutionalized in society."

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are "easy to manipulate as a result of their illness or socioeconomic condition." Care should be taken to avoid overburdening institutionalized persons who "are already burdened in many ways by their infirmities and environments." Nontherapeutic research that involves risk should use other, less burdened populations, unless the research "directly relate[s] to the specific conditions of the class involved."

The Belmont Report: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

Chapter 3 – CATEGORIES OF RESEARCH REVIEW

A. Full Board Review:

Full Board Review: Reviewed by a quorum of Board members.

Human subject research studies that are not classified as exempt require review by the full IRB at a convened meeting. Sterling IRB meetings are typically held twice a week, on Tuesdays and Thursdays, but may be cancelled by the Administrator for insufficient applications, holidays, or inability to secure a quorum.

Sterling IRB typically uses a primary reviewer system for full Board reviews. Submission application materials are typically sent to the Board at least 4 days prior to a meeting. When a primary reviewer is used, he/she leads the discussion of each project they reviewed and the Board determines whether the project meets the criteria for approval and whether revisions to the protocol or informed consent are needed.

The informed consent is reviewed for accuracy, clarity, and inclusion of the required elements of consent. By a majority of those present at the meeting, each study is either: (1) approved as submitted; (2) approved pending satisfaction of Board-determined contingencies; (3) deferred pending review at a subsequent Board meeting after receipt of significant additional information or revisions; or (4) disapproved. Notification will be made within 24 hours and approval documents will usually be mailed within 2 business days.

B. Expedited Review:

Federal regulations recognize that certain aspects of research may be reviewed by an IRB through an expedited review procedure (45 CFR 46.110) (21 CFR 56.110). Sterling IRB employs the expedited review procedure for minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Expedited review means that the IRB Chairman or designee is solely responsible for the review and approval. Expedited review approval documents will usually be mailed within 2 business days. The Board will be apprised of research items approved by expedited review.

C. Exempt Human Subject Research:

Certain types of human subject research that present little or no risk to the participants may be classified as exempt from the federal regulations (45 CFR 46.101(b)) (21 CFR 56.104). The Chairman or designee will determine whether the research meets the exempt criteria, based on review of the correspondence concerning the request, protocol, and associated documents. The decision will usually be communicated to the Principal Investigator within 48 hours of the determination being made.

Chapter 4 – PRINCIPAL INVESTIGATOR RESPONSIBILITIES

A. Study Conduct:

The Principal Investigator is responsible for the ethical conduct of the research study, and for protecting the health and welfare of all subjects enrolled at his/her site(s). The clinical research study must be conducted as stated in the protocol and in accordance with all applicable federal, state and local laws and Good Clinical Practices (GCP). It is expected that the investigator have the resources necessary to protect human participants, including sufficient time to conduct and complete the research, as well as access to a population that will allow recruitment of the necessary number of participants.

The investigator should be familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigator's brochure, in the product information and in other information sources provided by the sponsor. Furthermore, it is expected that the investigator follow the study's randomization procedures, if any, and that they ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding. The Principal Investigator agrees to abide by the Investigator Compliance Agreement as stated in the Submission Application for the Investigator/Site. (*See the Sterling IRB website <www.sterlingirb.com>*)

B. Training and Education / Investigator and Study Staff Qualifications:

The Principal Investigator and all key research personnel should have appropriate training in conducting clinical trials and each should be aware of the obligations to communicate with the IRB and the Sponsor during the study. (*See the Sterling IRB website <www.sterlingirb.com> for additional resources.*)

The investigator (PI, Sub-I(s)) is responsible for providing evidence of their qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB, or the regulatory authority.

While the Principal Investigator is ultimately responsible for the conduct of the research study, the PI may delegate research responsibility to appropriately qualified persons. However, they must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility. Further, the PI is responsible for maintaining a list of appropriately qualified persons to whom they have delegated significant trial-related duties.

C. Record Keeping:

The study records need to be retained as directed by the Sponsor and as required by applicable law and/or regulation. The Principal Investigator is responsible to maintain complete and accurate records for the following:

- Source records for each subject
- All correspondence with the Sponsor and IRB including, but not limited to, copies of the application, notices of approval, acknowledgements, and signed informed consent documents

D. Audits and Inspections:

All records of human subject research are subject to inspection by regulatory agencies, the Sponsor and Sterling IRB.

Sterling IRB also has the authority to conduct "for cause" and/or random audits of investigative sites under its review. Sterling IRB or an independent third party may observe the implementation and conduct

of human subject research activity under the IRB's review, including observance of the informed consent process, at any time.

At least once per quarter, Sterling IRB will randomly audit an active investigative site meeting one or more of the following criteria: 1) the study presents "greater than minimal risk" or is a study of a "significant risk" device; 2) the Investigator has or plans to enroll subjects from one or more vulnerable populations; and/or 3) the Investigator has or plans to enroll a large number of subjects as compared to the anticipated study-wide enrollment. For these randomly selected audits, Investigators will receive notice 2 weeks in advance of the scheduled audit.

The Principal Investigator is responsible for being prepared at all times for an audit or inspection.

E. Form FDA 1572:

The Principal Investigator is responsible for completing and submitting the Form FDA 1572 prior to the start of the study, if applicable. This is a contract between the Principal Investigator and the FDA which outlines the responsibilities that the Principal Investigator agrees to assume in order to conduct the study. All copies of the original and revisions to the Form FDA 1572 need to be forwarded to Sterling IRB.

F. Referral Fees, Incentives, and Bonus Payments for Recruitment:

1. Referral Fees: Sterling IRB does not support the recruitment of research subjects by payment for referrals to research subjects or other persons including, but not limited to, the Principal Investigator, Sub-Investigator or Clinical Coordinator(s) for research under its review. This is in accordance with the American Medical Association (AMA) Code of Medical Ethics which states, "Offering or accepting payment for referring patients to research studies (finder's fees) is also unethical." *E-6.03 Fee Splitting Referrals to Health Care Facilities*

2. Incentives and Bonus Payments for Recruitment: The Principal Investigator should report to Sterling IRB any proposed incentives, gifts, or bonus payments to the Principal Investigator or study staff other than the original contractual agreement for review. These will be reviewed on a case by case basis. Sterling IRB is concerned that these practices may cause undue influence on the research staff. *E-8.0315 Managing Conflicts of Interest in the Conduct of Clinical Trials*

G. Summary of Requirements of the Principal Investigator:

The Principal Investigator is required to provide the following information and reports to Sterling IRB. These requirements should be reviewed by all individuals involved in the research activities. If you have any questions, please call Sterling Institutional Review Board at 888-636-1062 and a member of our staff will be glad to assist you.

- **Amendments:** Once a study has received initial IRB approval, any change to the study is considered an amendment. All amendments must be submitted to Sterling IRB for review and approval prior to implementation, unless to eliminate immediate hazards to subjects, in which case the IRB must be notified immediately.
- **Informed Consent:** All changes to the informed consent are considered an amendment to the study and must be reported to Sterling IRB. Approval must be granted by Sterling IRB prior to use of the revised informed consent.
- **Advertisements and Recruitment Material:** These items are reviewed in accordance with FDA guidelines, and must be approved by Sterling IRB prior to use. Approved submissions will be stamped "approved." Once an Investigator has received initial IRB approval, any advertisements and

recruitment materials submitted for approval thereafter are considered amendments and must be accompanied by a completed Modifications and Amendments Submission Form. **Forms can be found at <www.sterlingirb.com>.**

- **Revisions to 1572:** Revisions to the FDA 1572 Form must be submitted to Sterling IRB. If the revised 1572 is due to a change of site/additional site, the revised FDA 1572 must be accompanied by a completed Add or Change Site Submission Application. **Forms can be found at <www.sterlingirb.com>.**
- **Serious Adverse Event Report:** Sterling IRB requires that the Serious Adverse Event Report be submitted if the event is unexpected, and serious. A *serious* event is one which occurs to a subject while participating in the study that: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; is a congenital anomaly/birth defect; results in persistent or significant disability/incapacity; requires intervention to prevent one of the aforementioned outcomes; or should be (in the Investigator's opinion) considered by the IRB. Note: questions regarding whether an event is considered an SAE can often be resolved by referring to the description of an SAE in the Protocol or consulting with the Sponsor. An *unexpected* event is an event, the nature or severity of which is not consistent with the potential risks in the Informed Consent Document(s), Protocol, Investigator's Brochure (IB), or Investigation Plan. The serious unexpected event should be reported **within 10 business days** of the Investigator's knowledge of the event. All fatal or life threatening events should be reported to Sterling IRB immediately. **Forms can be found at <www.sterlingirb.com>.**
- **Significant Protocol Deviation Report:** Sterling IRB requires that all significant protocol deviations are to be reported **within 10 business days** of when the site becomes aware of the study event. Sterling IRB defines significant deviations as those that: (1) affect the scientific design/integrity of the study; (2) affect the rights, safety, or welfare of study subjects; (3) change the risk/benefit ratio; or (4) violate an ethical principle. Non-significant deviations do not need to be reported to the IRB unless the Sponsor/site SOPs require the Investigator to do so. **Forms can be found at <www.sterlingirb.com>.**
- **Unanticipated Problems (Other):** There may be other unanticipated problems (that do not fall within the classifications for SAEs, External SAEs or Significant Protocol Deviations) but which: (1) involve risk(s) to the research subject(s) or others; (2) affect the rights, safety or welfare of study subjects; (3) affect the scientific design/integrity of the study; (4) change the risk/benefit ratio; or (5) violate an ethical principle. Unanticipated Problems may include problems that affect privacy (e.g., an unauthorized person gaining access to confidential study records), or safety (e.g., the disappearance of study medication). All Unanticipated Problems should be reported **within 10 business days** of the site becoming aware of the problem. **Forms can be found at <www.sterlingirb.com>.**
- **Sponsor-Granted Exceptions:** Sterling IRB requires that all Sponsor-granted protocol exceptions that may affect the scientific design/integrity of the study, affect the rights, safety or welfare of study subjects, or change the risk/benefit ratio, must be reported to the IRB for IRB approval *prior to implementation*, except where necessary to eliminate apparent immediate hazard to human subject(s). Exceptions must be submitted to the IRB accompanied by documentation of the Sponsor's approval thereof. Additionally, when the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required [21 CFR 812.150 (4)]. Exceptions necessary to eliminate apparent immediate hazard to human subjects should be reported promptly after initiation. **Forms can be found at <www.sterlingirb.com>.**
- **Continuing Review Reports:** All reports minimally include the current study status, the number of subjects consented and their status, a current risk-benefit assessment based on study results, audit and monitoring report information, change in community attitudes, and any new information since the IRB's last review. **Forms can be found at <www.sterlingirb.com>.**

A reminder will typically be sent prior to the due date, but it is primarily the Principal Investigator's responsibility to ensure that all required continuing review reports are timely submitted.

- **Site Interim Status Update:** An Interim Status Update should be filed for the interval that was established by the IRB at the time of approval (if applicable).
- **Site Continuing Review Status Report:** An Investigator must receive continuing review approval prior to the “study expiration date” listed on the initial or renewal approval documents. The Investigator should submit the Site Continuing Review Status Report not less than one month prior to the last Sterling IRB meeting preceding the expiration date. ***Federal regulations do not allow the IRB to grant extensions or grace periods, so timely submission of the Site Continuing Review Status Report is important to avoid unnecessary interruptions in the study.***
- **Site Final Report:** After the last subject has completed the study and the Sponsor/CRO has indicated that the study is completed at the site, the Site Final Report must be submitted to ensure proper closeout. This report should include the date that the final subject completed the study. A Site Final Report should also be filed in the event of cancellation or termination of a study.
- **Investigator Noncompliance:** The Investigator and study staff must report noncompliance with the study protocol and procedures, and rules and regulations governing research (i.e. state and federal regulations, IRB policies and procedures, etc.) to the IRB. The IRB will review the reported concern and will determine whether instances of noncompliance constitute serious or continuing noncompliance. The IRB will report any instance of an Investigator’s serious or continuing noncompliance with the requirements of the FDA (and other agencies, if applicable) and/or IRB, as set forth in the Federal Regulations and/or Sterling IRB Standard Operating Procedures, by notice to the Investigator, Sponsor and the regulatory agency.
- **Investigator to Withdraw from Study:** Notification of the Investigator’s decision not to conduct the study or to withdraw from the conduct of the study must be submitted to the IRB. A Site Final Report will need to be filed unless a new Investigator has been approved to continue with the study site.
- **Termination or Suspension of a Study:** Notification to the IRB of the Sponsor’s termination or suspension of a clinical study. Also, withdrawal of approval from another IRB.

Chapter 5 – SUBMISSIONS TO THE IRB

A. New Study Submissions:

Principal Investigators are required to submit the Submission Application for the Investigator/Site (and attachments) along with the requested items listed on the Submission Guidelines. Instructions for completing the form are self-contained. All forms and guides are located on the Sterling IRB website <www.sterlingirb.com> and can be filled in electronically. If there are any questions, our staff will be glad to assist you.

B. Change in Principal Investigator:

When there is a change of Principal Investigator for an already approved study, the following is required to be submitted to Sterling IRB for review of the new Principal Investigator:

- Submission Application for Change of Principal Investigator
 - Note, this form may be used **only** if the new Principal Investigator will continue to conduct the study using only the procedures already approved, at only the site(s) already approved, using only the research personnel already reviewed (however, this form may still be used if there is a change in subject compensation). Otherwise, a Submission Application for the Investigator/Site is required to request a change of Principal Investigator.
- Copy of the revised Form FDA 1572, if applicable
- CV of the new Principal Investigator
- Copy of the new Principal Investigator's medical license (wallet card is acceptable)
- Copy of the new Principal Investigator's DEA registration, if applicable

C. Change in Sub-Investigator(s):

When there is a change in the Sub-Investigator(s) for an already approved study, the following is required to be submitted to Sterling IRB:

- Cover letter noting to which study the changes apply, including contact information for the site.
- Copy of the revised Form FDA 1572, if applicable
- CV of the Sub-Investigator(s) (if modification involves the addition of a new Sub-Investigator)

D. Change in Site or Adding Additional Sites:

When there is a change in site location or additional sites are added, the following is required to be submitted to Sterling IRB:

- Add or Change Site Submission Application for each site that has changed or been added to the study
- Copy of the revised Form FDA 1572, if applicable

E. Translations for Subject Information and Informed Consent:

Informed consent must be presented in a language understandable to the subject. If the subject does not speak English, Sterling IRB requires a certified translation of the IRB approved informed consent. Some Sponsors require back translations for accuracy. All revisions of the informed consent must go through

the certified translation process, however Sterling IRB may make minor changes without going through the certification process.

Sterling IRB can arrange to have the informed consent and any other study related document translated into any language. As an alternative, the site or study Sponsor can submit a document that has already been translated along with a certification statement for verification to Sterling IRB.

F. Advertisements and Recruitment Materials:

Advertisements and recruitment materials may be submitted to Sterling IRB for review by regular mail, fax, or e-mail: info@sterlingirb.com. Advertisements and recruitment materials submitted for review after the Investigator has received initial approval are considered amendments and must be accompanied by a completed Modifications and Amendments Submission Form. Include the IRB ID# on all documents.

Advertising or recruiting for study subjects is considered to be the start of the informed consent process. **The information contained in the advertisement/recruitment materials and the mode of communication must be reviewed by the IRB and approved before they are used.** All submitted materials must comply with applicable federal regulations, and state and local laws. Furthermore, it is Sterling IRB's expectation that the recruitment processes which are employed by the Principal Investigator and the research staff are fair and equitable.

Sterling IRB requirements for advertisements and recruitment materials:

- Purpose of research is stated
- Does not state or imply a certainty of favorable outcome beyond what is outlined in the consent document and the protocol
- Statement that the information provided pertains to a research study
- Contact information should be included
- Must not be coercive
- Compensation must not be emphasized (e.g., by such means as larger or bold type)
- Compensation explained if greater than \$1000
- Does not allow compensation for participation in a trial to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing (FDA-regulated research)
- Must not include testimonials (defined as a statement in support of a particular truth, fact, or claim). Recruitment materials cannot contain statements that explicitly or implicitly make effectiveness claims about the investigational product or procedure. Testimonials, in general, advertise the product or procedure that they discuss in the words of a "satisfied user," and so, by their very nature, are claiming success, improvement, and/or effectiveness. Should not use the terms: "state of the art," "cutting edge," "breaking technology," or "improved."
- Does not make claims, explicitly or implicitly, that the test article is known to be equivalent/superior to any other drug, biologic, or device
- Does not make claims, explicitly or implicitly, that the test article is safe/effective for the purpose under investigation
- Benefits are included but not guaranteed
- Must not use the word "free" when referring to procedures and medications that may be received as a part of participation in the research study. Acceptable language would be, "at no cost," or "at no charge."
- Does not contain the word "new" when referencing the test article, unless qualified as investigational
- The word "earn" should not be used
- Must define the word "placebo" (if used)
- For pediatric studies, advertisements should be directed at adults
- Does not include coercive language, tone, or exculpatory language

For print advertisements, please submit a copy of the print ad in the format that it will appear, so that Sterling IRB can review the layout of the advertisement as well as the text. If you are submitting

advertisement recruitment materials with a reference or link to a website, any research-related content, including any information which pertains to a study under the review of Sterling IRB, must be submitted to the IRB for review and approval prior to use. It is your responsibility to ensure that your submission includes any web content which requires IRB review.

Sterling IRB does not require the submission of, but will review upon request, website recruitment content where the system format limits the material presented to basic trial information, such as the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and information on how to contact the site for further information. Examples of such listings include content posted to government-sponsored sites, such as the National Institutes of Health (NIH) ClinicalTrials.gov website, the NIH National Cancer Institute's cancer clinical trials listing (PDQ), and the AIDS Clinical Trials Information Service (ACTIS). However, Sterling IRB does require the submission of web content where the opportunity to add additional descriptive information is not prevented by the system format, for review and approval prior to use.

It is your responsibility to ensure that links to external sites, which are contained within web submissions, are in compliance with applicable regulations and IRB requirements, as Sterling IRB does not review this material.

If participating in a large, multi-site study, the Sponsor may prepare a package of recruitment materials/advertisements for you to use once approved by the IRB. Each site choosing to use these recruitment materials should include their site specific information, such as the clinic name, telephone/contact information and compensation information, taking care not to alter the layout, type font or size of the approved advertisement. These recruitment materials/advertisements are considered approved, and **do not need to be re-submitted** to Sterling IRB.

Radio and television advertisement scripts must be submitted to Sterling IRB for approval. It is recommended that scripts are reviewed and approved prior to production of cassettes/CDs/MP3s for radio and videotapes/DVDs for television ads. All recruitment media (cassettes/CDs/MP3s for radio and videotapes/DVDs for television) must be approved before advertising begins.

Recruitment materials/advertisements provided with the **original submission** will be reviewed with initial review. Sterling IRB will notify you if any revisions are required before approval can be granted. Approved recruitment materials/advertisements will be provided in the initial approval documents, and will be marked with an "Approved" stamp.

Recruitment materials/advertisements submitted **after the Investigator's initial review** must be accompanied by a completed Modifications and Amendments Submission Form. These items usually will be reviewed by expedited review within 2 business days. Sterling IRB will notify the Principal Investigator or designee if any revisions are required before approval can be granted. Approval documents and the recruitment materials/advertisements that have been stamped "Approved" will be sent to the site.

Sterling IRB must review any revision made to previously approved recruitment materials/advertisements. These include text changes, and other image changes such as pictures, font type or size. Please contact Sterling IRB if there are any questions regarding changes to participant recruitment materials/advertisements.

G. Telephone Screenings:

Sterling IRB requires that a telephone screening script include the following information:

- The prospective subject must provide their permission for the screening to proceed and for the screener to collect confidential medical information (otherwise, the call should be ended)
- The prospective subject will be told that the information gathered from the screening procedure will be kept confidential
- The prospective subject will be told what will happen to the information collected (i.e stored in a database)

- The prospective subject will be told what will be done with the information if he/she does not qualify for this study (i.e. will the information be destroyed, or, with the permission of the prospective subject, will the information be kept in a database and used for another study. In the later case, the prospective subject **must give** his/her permission for the information to be stored)
- The prospective subject must be told that he/she does not have to answer any questions they do not want to respond to, and may choose to end the phone call at any time

Below is suggested telephone screening script confidentiality language:

“We are conducting a research study in which you may be eligible to participate. If you are interested, I will ask you some confidential questions regarding your medical history and present condition. You do not have to answer any questions that you do not want to respond to, and you may end this phone call at any time.

All information collected today will be kept confidential. I am using a paper survey, which will be destroyed if you decline participation. If you choose to participate in this study, this survey will be kept with other research records for this study. These records are accessible to our research staff and will not be shared with anyone else without your permission.”

“Are you interested in participating in this study?”

If answer is “no”, person should be thanked and call ended

If “yes”, proceed to next question:

“Do we have permission to proceed in obtaining the confidential medical information about your medical history and present condition?”

If answer is “no”, person should be thanked and call ended

If “yes”, proceed to the next question

“May we keep the information we obtain in a database in order to contact you regarding future studies?”
(*If applicable*)

If “yes”, information may be retained in a database for future studies

If “no”, information may not be retained in a database for future studies, although if the prospective subject qualifies, they may still participate in this study.

Note: See Chapter 8 Informed Consent; J. Informed Consent Requirements When Determining Eligibility for Research, for additional information.

HIPAA RESPONSIBILITIES: This is applicable to covered entities as defined in the Privacy Rule.

If Protected Health Information (PHI) is to be recorded into a database, the Principal Investigator will need to complete and submit an Application for Partial Waiver of Authorization - For Recruitment Purposes. See the Sterling IRB website <www.sterlingirb.com>. The completed Application should be submitted along with the telephone screening script for approval.

H. Amendments to Previously Approved Research:

Any change to previously approved research must be reviewed and approved by the IRB prior to implementation, excepting changes made to eliminate immediate safety hazards to participants, which must be immediately reported to the IRB.

1. Protocol Amendments - Sterling IRB offers two options for submitting Protocol amendments for IRB review:

Option 1

Submit a completed Modifications and Amendments Submission Form (see the Sterling IRB website <www.sterlingirb.com>), along with the following attachments:

- Copy of Protocol
- Copy of informed consent detailing proposed changes, if any
- Copy of 'Summary of Changes' or tracked version of protocol showing changes
- For device studies, a copy of the FDA IDE letter approving the amendment, if applicable
- Copy of questionnaires or surveys to be used with the study, if changed
- Copy of advertisements/recruitment materials, if changed

Option 2

Submit a cover letter detailing the request for an amendment to the protocol or an addition of another arm or treatment group to the protocol, along with the following:

- Copy of Protocol
- Copy of informed consent detailing proposed changes, if any
- Copy of 'Summary of Changes' or tracked version of protocol showing changes
- For device studies, a copy of the FDA IDE letter approving the amendment, if applicable
- Copy of questionnaires or surveys to be used with the study, if changed
- Copy of advertisements/recruitment materials, if changed

Protocol amendments must receive IRB review and approval before they are implemented, unless an immediate change is necessary to eliminate an apparent hazard to the subjects. The IRB should be notified of this occurrence immediately. If an amendment requires changes to the informed consent document, please follow the directions listed in section '2', Revisions to the Informed Consent Document, below.

2. Revisions to the Informed Consent Document - Sterling IRB offers two options for submitting revisions to the Informed Consent Document(s) for IRB review:

Option 1

Submit a completed Modifications and Amendments Submission Form (see the Sterling IRB website <www.sterlingirb.com>), along with copies of **both** the already-approved document **and** the proposed revised document. These should be submitted with changes clearly marked by red lining, highlighting, or tracking **both** the already approved document **and** the proposed revised document.

Option 2

Submit a cover letter requesting a revision to an already-approved informed consent document, along with copies of **both** the already-approved document **and** the proposed revised document. These should be submitted with changes clearly marked by red lining, highlighting, or tracking **both** the already approved document **and** the proposed revised document.

Consent revisions will be reviewed by the full Board unless the changes meet Sterling IRB's requirements for expedited review.

Any IRB approval of a revised informed consent document that might relate to the subjects' willingness to continue participation in the study will necessitate the re-consent of all current subjects (active or follow-up) in the study. Subjects who have completed the study and those in follow-up may be mailed a copy of the changes to the consent document. The FDA and Sterling IRB do not require the re-consenting of subjects that have completed their active participation unless information that has been received affects the risks to research subjects that have already completed the study.

3. Changes to the Investigator's Brochure:

The Sponsor may update the Investigator's Brochure (IB) during the course of the study. Changes to the Investigator's Brochure should be submitted to the IRB. If this is a multi-site study, the Sponsor will usually submit the revision on behalf of all the Principal Investigators participating in the study. Documentation of IRB review of the IB will be provided.

4. Change in Principal Investigator:

During the course of a study, the Principal Investigator may change. This change must be approved by the IRB prior to implementation. Please see our website for the appropriate form

5. Addition or Change in Study Site:

During the course of a study it might be necessary to close or add sites. This change must be submitted to the IRB for review and approval. Please see our website for the appropriate form.

6. Recruitment, Screening Scripts, or other study materials not submitted prior to the initial approval of a study:

All materials that will be used as part of a study must be reviewed and approved by the IRB prior to use. These materials can be submitted as part of the initial study protocol; however, many times these materials are not available at the time of the initial submission. Materials which are submitted following initial approval of a study must be submitted as an amendment. Please see our website for the appropriate form.

I. Forms:

Sterling IRB Forms are located on our website at <www.sterlingirb.com>. Sterling offers two ways to complete the forms for submission. The forms can be printed and manually completed or the electronic version can be completed online, saved and printed. All forms must be submitted with an authorized signature. The electronic version is compatible with Microsoft Word 2000 and above.

The Submission Application for the Investigator/Site is completed when a Principal Investigator/Site first seeks IRB approval. If additional research sites are submitted **concurrently** with the first Principal Investigator/Site, a Supplemental Site Form must be completed and submitted for each additional research site.

Once a Principal Investigator has been approved, any **subsequent** changes/additions in research sites must be submitted for approval by completing an Add or Change Site Submission Application (accompanied by the revised FDA 1572, if applicable).

For a change in Principal Investigator for an already-approved site, submit a completed Submission Application for Change of Principal Investigator. Note: the Submission Application for Change of Principal Investigator can only be used if the new PI will continue to conduct the study using only the procedures already approved, at only the site(s) already approved, using only the research personnel already reviewed (though the form may be used if there is a change in compensation). Otherwise, a completed Submission Application for the Investigator/Site should instead be submitted.

J. Criteria for IRB Approval of Research:

Only those research submissions which (at least) satisfy the criteria for IRB approval of research as outlined in 21 C.F.R. 56.111 and/or 45 C.F.R. 46.111 (as applicable) will be approved by the IRB. These criteria are as follows:

- 1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever

appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- 2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. 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 that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- 3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.
- 4) Informed consent will be sought from each prospective subject or the subject's legally acceptable representative, in accordance with and to the extent required by regulation.
- 5) Informed consent will be appropriately documented, in accordance with and to the extent required by regulation.
- 6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- 7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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

K. Notification of Approvals and Acknowledgements:

- Full Board Review of a New Study: Sterling IRB will contact the Sponsor/CRO and/or Principal Investigator typically within 24 hours of the meeting with a notification of the Board's decision. Approval documents will usually be sent within 2 business days.
- Expedited Review (of minor changes to previously approved research): Approval documents will usually be sent within 2 business days of approval.
- Amendment to Add a Principal Investigator: Approval documents will usually be sent within 2 business days of approval.
- Advertisements and Recruitment Materials: Items are usually reviewed by expedited review within 2 business days.
- Serious Adverse Events: Acknowledgements will usually be sent within 15 business days of Sterling IRB's review.
- Significant Protocol Deviations: Acknowledgements will usually be sent within 15 business days of Sterling IRB's review.
- Sponsor-Granted Exceptions: Approval documents will usually be sent within 5 business days of approval.
- Unanticipated Problems: Acknowledgements will usually be sent within 15 business days of Sterling IRB's review.
- External Adverse Events (INDs): Acknowledgements will usually be sent monthly.

- Site Continuing Review Status Report: Approval documents will usually be sent within 7 business days of Sterling IRB's review.
- Site Interim Status Update: Acknowledgments will usually be sent within 15 business days of Sterling IRB's review unless the IRB requests clarification or additional information.
- Site Final Report: Acknowledgements will usually be sent within 15 business days of Sterling IRB's review.

(All documents are sent through the U.S. Postal service unless otherwise requested. Overnight delivery service will be billed at cost, if requested.)

Chapter 6 – CONTINUING REVIEW

Continuing review of IRB approved research is required under 45 CFR 46.109(e) and/or 21 CFR 56.109 (f). The period for continuing review is determined by the IRB; however, it must occur at least annually.

The Continuing Review, Interim, and Final Reports require information about the number and status of subjects involved in the study. The categories are defined below:

- **Total Consented:** The number of prospective subjects that have signed the consent form. Subjects must sign the consent form prior to screening, with the exception of verbal consent for telephone screenings.
- **Screen Failures:** The number of consented subjects who will not be able to participate in the study because of information gathered, including test results that were obtained, during the screening process.
- **Total in Screening/run-in:** The number of prospective subjects that have been consented and are currently in the inclusion/exclusion phase of the study.
- **Total Active:** The number of randomized subjects (those that have passed the screening process) who are currently active in the study. Subjects that are in follow-up are considered to be active.
- **Total Completed:** The number of subjects who have completed all study requirements and are no longer in follow-up (all subject contact is completed).
- **Total Subjects Withdrawn/Terminated Early*:** The number of randomized subjects that withdrew or were withdrawn prior to completion (e.g. lost to follow-up, terminated by the sponsor, transferred to another study site, withdrew consent, discontinued due to an adverse event, unanticipated problem, or protocol deviation, non-compliance (specify how), etc.).
**Please note, although the study subject is not obliged to give their reason(s) for withdrawing prematurely from a clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the subject's rights.*

Total Consented should equal Total Screen Failures + Total in Screening/run-in + Total Active + Total Completed + Total Withdrawn/Terminated Early.

Site Continuing Review, Interim and Final Report forms are located on the Sterling IRB website <www.sterlingirb.com>.

A. Continuing Review Status Report: (Application for Continuation)

Sterling IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. All non-exempt research projects will receive full Board continuing review. It is the responsibility of the IRB to perform a substantive continuing review and consider the same issues as during initial review.

It is the Principal Investigator's responsibility to submit the Site Continuing Review Status Report in sufficient time to permit review and approval prior to the study expiration date. **The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval.** Continuing review and reapproval of research must occur on or before the one year anniversary of the initial IRB approval date. To assist in this Principal Investigator obligation, Sterling IRB will typically send reminder notices (*via fax /or mail /or e-mail*). **It is important to remember that the IRB needs to receive the Continuing Review Report in sufficient time for review and re-approval of the research prior to the study expiration date. It is recommended that the Continuing Review Reports be submitted not less than 30 days prior to the study expiration date.**

If the Principal Investigator does not submit a Site Continuing Review Status Report in time for Sterling IRB review prior to the expiration date, he/she will be notified by memorandum that the IRB approval has lapsed. This memo details that all recruitment and study related activities (advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information), including data analysis, **must stop**. One exception would be if the cessation of treatment poses a threat to the life or welfare of a subject. If continuation of research procedures is necessary for subject safety, the IRB must be notified **immediately**. Failure to submit for renewal may result in Board action(s) including, but not limited to, suspension and/or termination of IRB approval or a finding of serious and/or continuing noncompliance.

Sterling IRB will send continuing review approval documentation to the study site which includes the study expiration date as well as the due dates for the Continuing Review reports. Continuing Review forms are available on the Sterling IRB website <www.sterlingirb.com>.

B. Interim Status Update:

The Board will determine intervals for review based on risk. These report forms are located on the Sterling website <www.sterlingirb.com>; the due date for these reports will be included in the approval letter (note, an Interim Status Update is not necessarily required by the IRB for all studies).

It is the Principal Investigator's responsibility to submit the Site Interim Status Update prior to the due date. To assist in this Principal Investigator obligation, Sterling IRB will typically send reminder notices (*via fax /or mail /or e-mail*). Please note, failure to submit an Interim Status Update (if required for the study) may result in Board action.

Following review, an acknowledgement will be sent to the investigator/site. (Effective 04/17/08)

C. Final Report:

After the last subject has completed the study and the Sponsor/CRO has indicated that the study is completed at the site, the Principal Investigator must submit a Site Final Report to the IRB to ensure proper closeout. This report should include the date that the final subject completed the study. This report must also be submitted when/if the study is cancelled or terminated. Furthermore, it is the responsibility of the investigator to also inform the regulatory authority with any reports which are required.

Following review, an acknowledgement will be sent to the investigator/site.

Chapter 7 – REPORTABLE EVENTS

Many types of events must be reported to the IRB. In general, events that are unanticipated and increase the risk to subjects or others, which may significantly affect the conduct of the clinical trial, which could affect a participant's willingness to continue in the study, or could be noncompliance, must be reported to the IRB. It is the IRB's responsibility to determine whether or not an event is an unanticipated problem involving risk to subjects or others and to notify the investigator of what steps, if any, are necessary to continue the study.

Unanticipated Problems Involving Risk to Subjects or Others are considered, in general, to include any incident, experience, or outcome that meets the following criteria:

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

A. Protocol Deviations:

Protocol deviations are study events where the Sterling IRB-approved research protocol has not been followed. The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected harm to subjects.

The Principal Investigator is responsible for reporting all significant deviations to the IRB; however data collection and communication of such events may be delegated to appropriate clinical site research personnel.

All significant protocol deviations should be reported within 10 business days of when the site becomes aware of the study event, using the Significant Protocol Deviation Report Form available on the Sterling IRB website at www.sterlingirb.com.

The Principal Investigator or Sub-Investigator will sign the Significant Protocol Deviation Report prior to submission to Sterling IRB.

DEFINITIONS:

Deviation: An unanticipated instance when the protocol, as currently approved, is not followed. Deviations can be separated into two categories, significant and non-significant (as defined below).

Significant Deviation: A protocol deviation that affects the scientific design/integrity of the study; affects the rights, safety, or welfare of study subjects; changes the risk/benefit ratio; or violates an ethical principle.

Examples of Significant Deviations:

- Enrolling a subject without obtaining informed consent
- Enrolling a subject outside the inclusion/exclusion criteria without sponsor approval
- Failing to send an exception report when enrolling a subject outside the inclusion/exclusion criteria with sponsor approval
- Deviations in the administration of study procedures (i.e. dosing/intervention errors)

- Willful or knowing misconduct on the part of the investigator(s) or study staff
- Breach in confidentiality/privacy pertaining to information about a subject
- Study drug missing at site or not returned by subject
- Study materials stolen (i.e. study drug, laptop containing study-related information)
- Subject on exclusionary, disallowed or concomitant medications without sponsor approval
- Failure to send an exception report when a subject is taking exclusionary, disallowed or concomitant medications with sponsor approval
- Failure to collect/perform labs or tests (i.e. chemistry, pregnancy, urine, ECG, EKG)
- Pregnancy
- Study drug given to incorrect subject
- Performing tests on a subject prior to consenting that subject
- Enrolling a subject before their screening lab(s) is/are received
- Consenting a subject with the incorrect version of the ICF
- Failure to initial a page of the Informed Consent Form
- Omission or delay of safety monitoring procedures, reports, or letters
- Untimely reporting of events to the IRB (i.e. not reporting Serious Adverse Events and Significant Protocol Deviations within 10 business days of the investigator's knowledge of the event, not reporting planned protocol exceptions for IRB Approval prior to implementation)
- Storing drugs incorrectly/at incorrect temperature
- Increase in enrollment not in accord with the protocol

Non-Significant Deviation: A protocol deviation that affects only logistical or administrative aspects of the study, has no substantive effect on the safety or well-being of research participants, does not affect the value of the data collected (meaning the deviation does not confound the scientific analysis of the results), and does not result from willful or knowing misconduct on the part of the Investigator(s). These deviations do not need to be reported to the IRB unless the sponsor/site SOPs require the Investigator to do so.

Examples of Non-Significant Deviations:

- Subject out of window (unless by a significant amount)
- Subject diaries/e-diaries not filled out/completed
- Principal Investigator signed in incorrect place/incorrect time on ICF
- Missed telephone calls, follow-up calls or contacts; out of window phone calls

Sponsor monitors often request that the site send the entire Protocol Deviation/Violation Log. Sterling requires submission of only significant deviations using the above criteria. Significant deviations should be submitted on the Significant Protocol Deviation Report that can be found on the Sterling IRB website at www.sterlingirb.com (with supporting documentation as applicable).

All Significant Protocol Deviations will be reviewed and acknowledged.

B. Serious Adverse Events (SAEs):

The Principal Investigator is responsible for reporting unexpected Serious Adverse Events (SAEs) to Sponsors and Sterling IRB; however, he/she may delegate the data collection and communication of such events to appropriate clinical site research personnel. The Principal Investigator or Sub-Investigator must sign the completed Serious Adverse Event Report form prior to submission to the IRB. **Sterling IRB requires that all unexpected Serious Adverse Events (SAEs) be submitted within 10 business days of the investigator's knowledge of the event. All fatal or life threatening events should be reported immediately to Sterling IRB. All unexpected Serious Adverse Events (SAEs), including fatal or life threatening events should be immediately reported to the Sponsor.**

Follow-up Reports: For all initial SAE reports that do not show resolution, Sterling IRB requests a follow-up report with additional information, including date resolved. More than one follow-up report may be sent to the IRB with information as it becomes available.

For unexpected serious adverse drug reactions, the Principal Investigator is responsible for following regulatory requirements related to the reporting of such events to the regulatory authority and the IRB.

For reported deaths, the Principal Investigator or designee should supply the Sponsor and IRB with any additional requested information (e.g., hospital records and autopsy reports).

DEFINITIONS:

Serious Adverse Event: An incident which occurs to a subject while participating in the study that: results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; is a congenital anomaly/birth defect; results in persistent or significant disability/incapacity; requires intervention to prevent one of the aforementioned outcomes; or should be (in the investigator's opinion) considered by the IRB. Note: Questions regarding whether an event is considered an SAE can often be resolved by referring to the description of an SAE in the protocol or consulting with the Sponsor.

Unexpected: An event, the nature or severity of which is not consistent with the potential risks in the Informed Consent Document(s), Protocol, Investigator's Brochure (IB), or Investigational Plan.

Upon receipt and review of an SAE, Sterling IRB may request additional information from the Principal Investigator. If Sterling IRB determines, after review of an SAE that additional information should be provided to the subjects, a request will be made to the Sponsor and Principal Investigator for a revision or addendum to the informed consent.

All Serious Adverse Events will be reviewed and acknowledged.

C. Unanticipated Problems (Other):

"Other" Unanticipated Problems include any unanticipated problem that does not fall within the classifications for Serious Adverse Events, External Serious Adverse Events, or Significant Protocol Deviations, but which: involves risk(s) to the research subject(s) or others; affects the rights, safety or welfare of study subjects; affects the scientific design/integrity of the study, changes the risk/benefit ratio; or violates an ethical principle.

The Principal Investigator is responsible for reporting Unanticipated Problems to trial Sponsors and Sterling IRB; however, he/she may delegate the data collection and communication of such events to appropriate clinical site research personnel. The Principal Investigator or Sub-Investigator will sign the Unanticipated Problem Report prior to its submission to Sterling IRB. **All unanticipated problems involving risk to subjects or others should be reported to Sterling IRB within 10 business days of the site becoming aware of the problem.**

Examples of unanticipated problems involving risks may include, but are not limited to the following:

- Unexpected frequency or severity of expected adverse events
- Incarceration of a study subject
- New findings that may influence a subject's willingness to continue participation in the study
- Subject complaints
- Breach of confidentiality or privacy
- Unauthorized use or disclosure of Protected Health Information (PHI)
- Study drug or test article accountability discrepancies
- Adverse results from a Data Monitoring Committee (DMC)
- Unanticipated legal risk to a subject
- Unanticipated additional costs to subjects

All Unanticipated Problems will be reviewed and acknowledged.

D. External Adverse Events (IND Safety Reports*):

External adverse events involve study participants who are not enrolled at a study site approved by Sterling IRB or where the Principal Investigator (PI) is not under the oversight of Sterling IRB. The Principal Investigator typically receives notification of these external events from the Sponsor in the form of an IND Safety Report.

* *The term “IND Safety Report” is used here to represent all types of external adverse events reports, including, but not limited to, IND Safety Reports, MedWatch Reports, Data Safety Monitoring Board Reports, and FDA Safety Alert Letters.*

IND Safety Reports should be submitted to Sterling IRB only if, in the opinion of the Sponsor/CRO/SMO or Principal Investigator, the report meets **at least one** of the following conditions:

1. Information on the report affects the rights, safety, or welfare of all participants in the study.
2. The report is for a device study.
3. The report is being submitted per Sponsor or Site requirements.

For multi-site studies, Sterling requires the Sponsor to submit IND Safety Reports on behalf of the Investigators. **Investigators should not submit any IND Safety Reports to Sterling if reports are being submitted on their behalf.**

For single-site studies, it is the Principal Investigator’s responsibility to submit all IND Safety Reports that meet one of the submittal conditions listed above.

All IND Safety Reports concerning other sites that meet one of the submittal conditions above should be submitted to Sterling IRB within 10 business days of receipt.

Data Monitoring Committee reports and Sponsor monitoring reports should be made available upon request.

E. Sponsor-Granted Exceptions:

Protocol exceptions are planned changes from the Sterling IRB-approved research protocol that (unlike amendments) do not result in permanent revision to the research protocol.

The Sponsor and Principal Investigator are responsible for obtaining IRB approval of protocol exceptions that may affect the scientific design/integrity of the study, affect the rights, safety or welfare of study subjects, or change the risk/benefit ratio, **prior to implementation**, except where necessary to eliminate apparent immediate hazard to human subject(s). Additionally, when the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required [21 CFR 812.150 (4)]. Exceptions necessary to eliminate apparent immediate hazard to human subjects should be reported promptly after initiation.

All Sponsor-Granted Exceptions should be reported using the Sponsor-Granted Exception Report available on the Sterling IRB website at www.sterlingirb.com. **Exceptions must be submitted to the IRB accompanied by documentation of the Sponsor’s approval thereof.**

The Principal Investigator or Sub-Investigator will sign the Sponsor-Granted Exception Report prior to submission to Sterling IRB.

DEFINITION:

Exception: A protocol exception is a type of planned change to the Sterling IRB-approved research protocol that (unlike an amendment) does not result in a permanent revision to the research protocol. A protocol exception typically involves a single subject or, less commonly, a small group of subjects.

The Principal Investigator is responsible for obtaining prior Sponsor and IRB approval for protocol exceptions as detailed above, however data collection and communication of such events may be delegated to appropriate clinical site research personnel.

All Sponsor-Granted Exceptions submitted to the IRB will be reviewed. Those deemed appropriate for approval via expedited review will be processed for such approval. All other Sponsor-Granted Exceptions will receive full Board review.

F. Other Reportable Events and Safety Information:

The following events/information should be reported to Sterling IRB within **10 business days**.

- Complaints from research subjects (minor subject complaints that are adequately resolved by the research staff do not need to be reported)
- Adverse sponsor or regulatory agency audit or enforcement action
- Reports, publications, or interim results or findings
 - DMC or DSMB reports and recommendations
 - Regulatory Agency Public Health Advisory
- New or updated study product information
 - Revised Investigator Brochure
 - Revised label / Package Insert
 - Revised Device Manual
- Sponsor or regulatory agency recall / withdrawal / clinical hold

Chapter 8 – INFORMED CONSENT

A. The Process of Consent and Assent:

Informed consent for a research study is a process, not just a form and a signature. It includes the recruitment materials, verbal instructions, written materials, question/answer sessions, and the informed consent agreement documented by the subject's signature. Information must be presented in a manner that provides the subject sufficient opportunity to consider whether to volunteer. Furthermore, in the course of communication with a prospective subject or their legally acceptable representative, use of exculpatory language (anything through which the subject or the subject's legally acceptable representative is made to or appears to waive any of their legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence) should be avoided. This should occur in an atmosphere that minimizes possible coercion or undue influence. The fundamental purpose of IRB review and approval of the consent document is to protect the rights and welfare of human subjects.

Minors and individuals who are not competent to provide consent should be given the opportunity to assent (affirmational agreement) to participate in the research study. Sterling IRB usually requires that individuals who are unable to provide legally effective informed consent on their own, assent to participation whenever possible, and also sign and date a written informed consent / assent document. For research involving minors, Sterling's policy is that a separate documented assent must be obtained from all children ages 7–11; verbal assent must be obtained from all minors. The Sponsor may increase the required age range for a separate assent to either younger than 7 or older than 11. The assent should be written at an age appropriate level. All other minors will document assent using the consent form.

Informed consent must be presented in a language understandable to the subject (approximately at an 8th grade reading level), with all required elements of consent included. In addition, no consent document may include exculpatory language. The informed consent document is the written summary of the information provided to the subject and documents the fact that the process of consent occurred. The consent document should be revised if protocol changes warrant it or new safety information becomes available that affects the risks to the participants. All informed consent revisions must be approved by Sterling IRB.

B. Elements of Informed Consent:

The basic elements of informed consent are found in 45 CFR 46.116 and/or 21 CFR 50.25. Federal regulations require that all consent forms contain the following information:

- Introduction (with a statement that the study involves research)
- Purpose of the study
- Description of the study procedures (identifying any that are experimental)
- Expected duration of the subject's participation
- Potential risks or discomforts of participation
- Description of any benefits to the subject or others that may reasonably be expected from the study
- Alternatives that may be available to the subject
- Confidentiality of records description
- Compensation for injury statement (for greater than minimal risk studies)
- Contact persons for answers to pertinent questions about the study, the rights of the subject, and whom to contact in the event of a research related emergency
- Statement that participation is voluntary (no loss of benefits to which the subject is otherwise entitled)
- Statement of who may review their records during the course of the study: Sponsor, Regulatory agencies (DHHS, FDA), Research staff, IRB and all others that may apply
- Dated signature lines to permit verification that consent was obtained prior to participation in the study

It is important to include additional elements of information if they are applicable to the study. These include:

- Unforeseen risks statement
- Reasons for involuntary termination of participation (if applicable)
- Additional costs to participants (if applicable)
- Consequences for withdrawal (e.g., adverse health/welfare effects if any)
- New findings statement (to be provided if relevant)
- Number of subjects
- Compensation

C. Waiver of Informed Consent:

Sterling IRB may approve a consent procedure which alters some or all of the required elements or may waive the requirement to obtain informed consent. Requests for a waiver of informed consent must be accompanied by appropriate justification. In general, Sterling IRB expects that informed consent will be obtained from all subjects. However, under certain circumstances, an IRB can waive certain requirements for informed consent if the following criteria are met:

1. *Waiver of Documentation of Informed Consent: the regulations (45 CFR 46.117(c)) state that the IRB may waive the requirement for the investigator to obtain a signed consent form if it finds either:
 - a. the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from 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. The research is not FDA-regulated.; or
 - b. the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Please complete a *Waiver of Documentation of Informed Consent* application, which is located on our website <www.sterlingirb.com>.

2. *Waiver of Elements of Consent: The IRB may consider waiving the requirement for some or all of the elements of informed consent. The regulations state that informed consent may be waived in full or in part if the IRB determines that:
 - a. The research involves no more than minimal risk to the subjects;
 - b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - c. The research could not practically be carried out without the waiver or alteration; and
 - d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
 - e. The research is not FDA-regulated.

OR:

- a. The research or demonstration project is to be conducted by, or subject to the approval of, state or local governmental 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 possible changes in methods or levels of payment for benefits or services under those programs; and
- b. The research could not practicably be carried out without the waiver or alteration.

Please complete a *Waiver of Informed Consent* application, which is located on our website <www.sterlingirb.com>.

*Please note, with a few narrow exceptions, FDA regulations do not allow for the waiver of informed consent. The following exceptions are noted in Title 21, as follows:

- a. Documentation of informed consent may be waived if the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. (See 21 CFR 56.109(c))
- b. 21 CFR 50.23 and 21 CFR 50.24 outline other conditions where an exception from informed consent requirements may be granted.

D. Informed Consent and State Law:

State and federal law can differ in a number of ways that may impact the conduct of human subjects research.

Both FDA and DHHS define a *Legally Authorized Representative* as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in research procedures. Dependant upon applicable law, a Legally Authorized Representative could be a spouse, adult child, sibling, or someone who has been granted durable power of attorney. Sterling IRB adheres to the International Conference on Harmonisation's Guideline for Good Clinical Practice, and favors use of the term *Legally Acceptable Representative*, defined by the ICH as an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Both FDA and DHHS define *children* as persons who have not attained the legal age for consent (under the applicable law of the jurisdiction in which the clinical investigation will be conducted) to treatments or procedures involved in the research or clinical investigations.

Who may act as a Legally Acceptable Representative and what, if any, treatments or procedures a "child" can consent to without parental permission vary by local jurisdiction.

It is the responsibility of the Principal Investigator to provide to the IRB any special laws governing medical research, including HIPAA, in the state or community where the clinical investigation will be conducted.

E. Safeguarding Confidentiality & Protecting Privacy:

Confidentiality and loss of privacy are issues of primary importance in research. "Confidentiality" pertains to the use and disclosure of information (i.e. a subject's Protected Health Information (PHI)). The Principal Investigator must have plans to protect the subjects' identity as well as the confidentiality of the research records. Such plans can include any or all of the following measures: (1) ensuring that all persons who will have access to subjects' PHI have been educated on the HIPAA Privacy Rule; (2) ensuring that all persons who will have access to subjects' PHI have been trained on their respective site's policies relating to confidentiality; (3) requiring that all persons who will have access to subjects' PHI sign a confidentiality agreement or similar obligation to protect the confidentiality of subjects' PHI; (4) limiting access to subjects' PHI to only those persons who need to have access for study-related purposes; (5) using electronic safeguards (i.e. secure data network, limited access to electronic data, password protections) for PHI that is maintained electronically; (6) using physical safeguards (i.e. storage in a secure, locked area) for PHI that is maintained on paper; (7) removing names and other identifying information from research records; and (8) redacting the identities of study participants when research results are presented at meetings or in medical publications. Other methods of safeguarding confidentiality may also be used.

"Privacy" addresses the way(s) a subject is kept from the presence or observation of others and/or protected from unauthorized intrusion(s). The Principal Investigator must have plans to protect the subjects' privacy. Such plans can include any or all of the following measures: (1) limiting personal information collected from subjects to only that which is necessary for study purposes; (2) collecting subjects' personal information in a private setting/location; (3) conducting study-related activities and

procedures in a private setting/location; (4) using drapes or other physical barriers for subjects who must disrobe; and (5) leaving study-related phone messages for subjects only in voice mailboxes to which the subject has sole access. Other methods of protecting privacy may also be used.

Principal Investigators may obtain a Certificate of Confidentiality if a determination is made that the research is of such a sensitive nature that protection is necessary to perform the research. Certificates of Confidentiality protect the privacy of individuals in any federal, state, local, civil, criminal, administrative, legislative, or other proceedings. Also see Chapter 11, A. HIPAA.

F. Subject Compensation:

Compensation for participation in research should not be offered to the subject as a means of coercive persuasion but as a form of recognition for the investment of the subject's time and any other inconvenience incurred. In most cases, compensation should be prorated during the study, to avoid any impression that the investigator is coercing the subject to continue in the study or penalizing the subject for noncompliance with the protocol. Large lump sums at the end of the study are discouraged. These can be seen as an undue influence to the subject continuing in the study, even though they may wish to discontinue.

The Board gives special consideration to vulnerable populations where others are acting as their legally acceptable representatives, that decisions to participate are not based on monetary gain.

G. Recruitment:

Advertising and recruiting for study subjects is considered to be the start of the informed consent process. The information contained in the advertisement/recruitment materials and the mode of communication must be reviewed by the IRB and approved before they are used. Any subsequent modifications to approved recruitment materials must also be reviewed and approved by the IRB before use. The materials must be consistent with the IRB approved protocol and informed consent form for the research study and must comply with applicable state and local laws. (See Chapter 5 content regarding Advertisements and Recruitment Materials)

Sterling IRB does not want to discourage participation of any who may benefit from research. However, the Board wants to be assured that if special considerations and additional measures need to be taken, they will be implemented. (See Chapter 9 – Vulnerable Subjects, Additional Considerations and Protections)

H. Non-English Speaking Subjects:

The informed consent document and all subject materials need to be translated into a language that the subject can read and understand. The translation process is discussed in Chapter 5. The person obtaining the informed consent must be fluent in both English and the language of the subject. The Board recommends that the site have a staff member who is fluent in the subject's language available to translate questions and answers between the Investigator and the subject during the study.

I. Subject Contact with Sterling IRB:

It is the responsibility of the Principal Investigator to explain the role of the IRB to prospective subjects. The name and telephone number of the Sterling IRB Chairman are listed in each informed consent document; a subject may contact the IRB with any questions they may have regarding their rights as a research participant or with any complaints, concerns, or offers of input they may have about the study.

J. Informed Consent Requirements When Determining Eligibility for Research:

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of or in preparation for the research, it is part of the research. *FDA Information Sheet Guidances Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors 1998 Update regarding Screening Tests Prior to Enrollment.*

K. Signature Requirements:

Research Participant Signature: The study participant must sign and date the consent form. A copy of the consent document will be given to the person signing this document. In emergency, life-saving situations, consent may be waived, but the request must meet the requirements found under 21 CFR 56.109 (c).

Signature of Person Who Conducted the Informed Consent Discussion: The person who conducted the consent discussion must sign and date the consent form.

Investigator Signature: Sterling IRB does not require the signature of the investigator on a consent form, but will include this signature block at the request of the Sponsor or Investigator.

Witness Signature: Sterling IRB does not require the signature of a witness on a consent form, but will include this signature block at the request of the Sponsor or Investigator. Sterling IRB requests that the Sponsor or Investigator have written procedures explaining who may be a witness, and what the witness signature signifies. If a witness signature block is included on the consent form, it must be signed for each consent form, unless the written procedures of the Sponsor or Investigator allow otherwise.

Impartial Witness Signature: If a research subject or legally acceptable representative is unable to read the consent form because of blindness or illiteracy, an impartial witness should be present during the entire consent process, and should sign and date the consent form. Sterling IRB may include a signature block for an impartial witness if the sponsor or investigator indicates that the subject population includes subjects who cannot read. The impartial witness signature block should be left unsigned unless there is an impartial witness present for the consent process. The Sterling Board may request an impartial witness signature for certain studies. An impartial witness signature block should also be included if required by federal, state or local law.

Signature of Legally Acceptable Representatives (LARs): A legally acceptable representative is defined as an individual, or juridical or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in a clinical trial. For research studies that allow the enrollment of subjects who are not legally competent, the consent form will include a signature block for an LAR. If the subject is not legally competent, an LAR must participate in the consent process, agree to the subject's participation in the research, and sign the consent form. The IRB must approve the use of an LAR. If the research allows the enrollment of both subjects who are and are not legally competent, then the LAR signature block will be labeled when necessary. This signature block should only be signed if the subject is not legally competent.

Telephone Consent: Verbal telephone consent is not sufficient unless the IRB has granted a waiver of documentation of consent. However, it is acceptable to send the informed consent document by fax and conduct the consent interview over the telephone when the subject or LAR can read the consent as it is discussed and can provide to the investigator sufficient documentation verifying his/her identity. If the consent is signed, it can be sent back to the investigative site by fax. The consent with original signatures will be mailed or brought to the investigative site at the earliest opportunity and a copy will be given to the subject or LAR.

Initials: Sterling IRB requires that the research participant, minor subject's parents, or legally acceptable representative initial each page of the consent document.

Chapter 9 – VULNERABLE SUBJECTS, ADDITIONAL CONSIDERATIONS AND PROTECTIONS

For all vulnerable populations, please provide the IRB a detailed explanation of the additional measures taken by your site to ensure the safety and welfare of these potential research subjects. For example, subjects may be given additional time to consider participation, how capacity for consent will be determined, whether the consent of legally acceptable representatives is to be sought, whether assent should also be sought, whether an advocate or consent auditor should be required and if there will be appropriate follow-up if needed.

A. Children and Minors:

Federal regulations identify four categories of research that may be allowable for children as outlined in 45 CFR 46, Subpart D and 21 CFR 50, Subpart D. The first three categories may be approved by the IRB but the fourth also requires special federal approval.

The Categories are:

- 1) Research not involving greater than minimal risk. (45 CFR 46.404; 21 CFR 50.51)
- 2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR 46.405; 21 CFR 50.52)
- 3) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR 46.406; 21 CFR 50.53)
- 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR 46.407; 21 CFR 50.54)

When children are involved in research, the regulations require the assent of the child (who is capable) and the permission of the parent(s) or legally acceptable representative (LAR). Children should always be asked if they want to participate in the research and must affirmatively agree to participate. Sterling requires a separate documented assent for children 7 – 11 years of age. In certain studies, the IRB may waive assent requirements.

B. Pregnant Women and Fetuses:

Federal regulations at 45 CFR 46, Subpart B require that IRBs consider additional safeguards before approving research involving pregnant women, fetuses, or neonates.

C. Prisoners:

Prisoners, due to the lack of control of their circumstances, are considered to be at greater risk of being coerced into participating in a research study. Special care should be taken that:

- The compensation is not coercive
- The risks of participating would be acceptable to non-prisoner volunteers
- The selection of subjects is equitable and does not affect decisions regarding parole
- Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data are taken
- Adequate follow-up care will be provided, if needed

Only four categories of research are permissible under 45 CFR 46, Subpart C.

The IRB should be notified immediately if an enrolled subject should become incarcerated while participating in a research study. The protocol and consent document would need to be reviewed again with a prisoner representative present. Unless the IRB reapproves the research for the inclusion of the prisoner(s), the newly incarcerated individual must withdraw from the study.

D. Cognitively Impaired Persons:

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

In general, Sterling IRB will consider the inclusion of this vulnerable group only where they are the only appropriate subject population, the research question focuses on an issue unique to subjects in the population, and the research involves no more than minimal risk. Research involving greater than minimal risk may be acceptable where the research is therapeutic with respect to individual subjects (i.e. there is a benefit), and where the risk is commensurate with the degree of expected benefit. Note: Sterling IRB usually requires that cognitively impaired persons who are unable to provide legally effective informed consent on their own, assent (provide affirmative agreement) to participation whenever possible, and also sign and personally date a written informed consent / assent document.

The Principal Investigator is in the ideal position to determine if a subject has the ability to understand the implications of the decision to participate in research, and whether the subject is making a rational decision to participate and has the ability to follow the protocol. Since capacity to consent or the ability to withdraw may fluctuate, the investigator should have a process in place for the continued verification of a subject's understanding and willingness to continue participation throughout the study. If a subject regains the capacity to consent during the study, the investigator should obtain consent from the subject for continued participation. If a person could lose the capacity to consent during the course of the study, the investigator should have a plan to assess continued consent that includes an assessment of capacity, and that provides the subject with the opportunity to appoint a proxy and to provide guidance to the proxy regarding the types of research in which they would not like to participate now or in the future.

E. Traumatized and Comatose:

The manner in which research involving emergency care is conducted shall receive IRB consideration because the subjects' ability to provide informed consent is often severely compromised, and decisions about participation must be made in an expeditious manner and the patient's legally acceptable representative may not be available. Altered mental status may arise from trauma, shock, infection, psychological response (anxiety, grief, pain) or the effects of drugs.

OHRP regulations permit waiver of informed consent requirements only in the case of research that presents no more than minimal risk (see 45 CFR 46.116), though the regulation are not "intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state and local laws." FDA regulations permit exception from informed consent requirement for patients confronted with a life-threatening condition where there is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the patient's life (see 21 CFR 50.23).

F. Terminally Ill:

Terminally Ill: Those who are deteriorating from a life threatening disease or condition for which no effective standard treatment exists.

Research involving terminally ill patients presents additional concerns in that potential subjects tend to be more vulnerable to coercion or undue influence than healthy adult subjects due to their desire to seek treatment, and the research is likely to involve more than minimal risk. Special attention should be given to the informed consent process ensuring the risks and benefits are communicated clearly and in a manner that will neither create false hope nor eliminate all hope.

G. Educationally Disadvantaged:

Sterling IRB shall determine that adequate consideration has been given to the manner in which research involving the recruitment of subjects who are educationally disadvantaged are to be afforded additional protections against coercion and undue influence. This population is considered vulnerable because subjects might be less capable of understanding the nature and risks of the research and may be more subject to coercion.

Illiterate persons who understand English may have the consent read to them and make their mark if appropriate under state law. This may require two witness signatures (check with local policy and / or state laws).

H. Economically Disadvantaged:

For economically disadvantaged subjects, special consideration should be given to ensure that compensation (whether monetary or other enticements) is not presented in a manner which may be coercive or present undue influence. "Free care" and reimbursements can substantially affect the voluntariness of the decision to participate. Payment should not be contingent on completion of the study and should be prorated.

I. Additional Considerations – Inclusion of Women and Minorities:

Sterling IRB shall determine whether consideration has been given to the manner in which subjects are selected and assure that adequate provision has been made for the inclusion of women and minorities, whenever possible. The benefits and burdens of research should be distributed fairly within society and investigators should always seek racial and gender equity in the recruitment of subjects.

J. Additional Protections – Students, Employees and Normal Volunteers:

Students: Students who participate in research in their own student setting (university, medical school).

There can be many potential problems with student participation in research. It is important to ensure that consent is freely given and not coerced. Students may feel the need to agree to participate in research in order to receive favor with the faculty, academic credit, monetary compensation, better grades, employment, recommendations, or other reasons. Another concern with student research is confidentiality, due to the close nature of a college environment.

Guidelines should be established to ensure that confidentiality and coercion do not become areas of concern in the academic research setting.

Normal Volunteer: A healthy person who volunteers for medical research and for whom no therapeutic benefit can result from participation.

The altruistic motivation for the normal volunteer's agreement to participate in research heightens the concern for the risks to which such participants should ethically be exposed. Monetary payments should not be so great that they constitute an undue inducement. Any compensation that is offered should be commensurate with the time, discomfort, and risk involved.

Employees: Employees of the research center.

It is important to ensure that employees who volunteer to participate in research at a research center where they are employed are not coerced in any manner. Their decision to participate, or not to participate, should have no impact on their performance evaluations, job advancement, or employment status. Guidelines should be established to handle an injury or illness of an employee who is participating in research. Due to the close nature of a research environment, strict measures should be taken to ensure the confidentiality of an employee's study-related records. Many Sponsors do not allow employees of the research center to participate in a research study.

Chapter 10 – RESEARCH CONFLICTS AND NONCOMPLIANCE

A. Conflict of Interest:

Situations arise in which financial or other personal situations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting and reporting research. The evaluation for assessing a potential bias to the mandate of human subject protections is very important. Sterling IRB has a financial disclosure section as a part of its Submission Application for Investigator/Site. If any information provided in the financial disclosure section changes during the course of the study, or within one year after the last participant completed the study as specified in the protocol, Sterling IRB must be immediately notified.

The Principal Investigator has the responsibility to assess conflict of interest for each study, and re-assess throughout the study. If conflict of interest becomes an issue, a report should be made to the IRB.

OHRP has published a guidance for protecting research subjects from possible harm caused by financial conflicts of interest in research studies. The guidance document is entitled Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection.

The target audience includes investigators, IRB members and staff, institutions engaged in human subjects research and their officials, and other interested members of the research community.

The guidance is located at:
<http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf>

B. Suspension or Termination of IRB Approval:

The Sponsor and appropriate regulatory agency will be notified of any determination made by the Board to suspend or terminate approval of a research study or investigative site. The Principal Investigator will be sent a letter detailing the IRB's determination, and the length of suspension or termination of IRB approval. Any response from the Principal Investigator, Sponsor/CRO or regulatory agencies will be reviewed by the IRB.

C. Noncompliance and Complaint Reporting:

The Principal Investigator bears the ultimate responsibility for the conduct of the research study.

The Principal Investigator must comply with the IRB's policies and requirements (as set forth in the Investigator Compliance Agreement in the Submission Application for the Investigator/Site, in the Sterling IRB Investigator Handbook, and in any determination of the IRB) as well as all regulatory requirements on the federal, state and local level.

Information regarding noncompliance in research may come to the attention of the IRB in many different ways. Reports of noncompliance may arise from new submission applications, continuing review reports, internal audits, safety reports, complaints from subjects in research, concerns from research sites, reports of protocol noncompliance (including information from monitoring letters or sponsor correspondence), failure or repeated failures of the Principal Investigator to file requested reports to the IRB, whistleblower information, publications written by Principal Investigators without IRB approval of the referenced study(ies), and regulatory agency audit reports regarding an investigator or a study.

Investigators and research staff are required to report any observed, suspected or apparent noncompliance to the IRB. This refers to all noncompliance, not just serious or continuing noncompliance.

D. Appeal of IRB Decisions:

Should Sterling IRB disapprove a submission for a new study or amendment thereto (including disapproval of the qualifications of a Principal Investigator), disapprove a research study and/or Principal Investigator for continuing review, or suspend/terminate a previously-approved research study and/or Principal Investigator, the document forwarded to the Principal Investigator will include the notification and a statement of the reason for the Board's decision. The Principal Investigator may submit an appeal of the Board's determination(s). The appeal must be in writing, addressed to the Board Chairman, and received by Sterling IRB no later than one calendar month following the Board meeting at which the determination was made. The appeal must include adequate supporting information to justify the Board's reconsideration of the matter.

The written appeal will be submitted to the full Board, and the Board members may vote to accept or reject it. It is within the discretion of the Chairman to allow the Principal Investigator to present the appeal in person or via tele/video-conference, and arrangements for this must be made in advance of the Board meeting.

In the event that an appeal is not received within one calendar month of a Board determination, or the convened Board reviews the appeal and declines to change its prior determination, the Board's original determination is final.

Neither the Principal Investigator, Institution nor Sponsor has the authority to overrule the IRB's disapproval or suspension/termination of a study or activity.

Chapter 11 – SPECIAL TOPICS

A. HIPAA

HIPAA stands for the Health Insurance Portability and Accountability Act of 1996. The Privacy Rule establishes the conditions under which certain healthcare groups, healthcare clearinghouses, organizations, or businesses, called “covered entities,” handle the individually identifiable health information known as Protected Health Information (PHI). Principal Investigators should be aware of the Privacy Rule because it establishes the conditions under which covered entities can use or disclose PHI for research purposes. The specific regulations for HIPAA are found in: 45 CFR 160 and 164.

Many research organizations that handle PHI will not have to comply with the Privacy Rule because they are not covered entities. The Privacy Rule will not directly regulate researchers who are engaged in research within organizations that are not covered entities even though they may gather, generate, access, and share personal health information. For instance, entities that sponsor health research or create and/or maintain health information databases may not themselves be covered entities; however, the Privacy Rule may affect their relationships with covered entities. It is recommended that research sites consult their own legal counsel to determine if they are a “covered entity”. See the decision tool entitled “Covered Entity Charts” available at:

<http://www.cms.hhs.gov/HIPAAGenInfo/Downloads/CoveredEntitycharts.pdf>.

Covered entities are permitted to use or disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances as set forth in the Privacy Rule.

Authorization by Research Participant:

HIPAA specifies that a covered entity may neither use nor disclose PHI for research purposes unless the patient has provided, in advance, his or her written authorization for such use or disclosure (unless a waiver is obtained). Authorization may be combined with the informed consent document. California requires the individual authorization to be a separate document with its own signature lines. It is the responsibility of the PI to be aware of any state and local laws that raise the standard that HIPAA has set forth.

Six Required Elements:

- A description of the PHI to be used or disclosed that specifically identifies the information
- Name of the persons and/or entities authorized to use or disclose the PHI
- Name of the persons and/or entities authorized to receive the PHI
- The purpose of the requested use or disclosure of PHI
- An expiration date, which may be indicated as “end of study” or “none,” for Authorization to place PHI in a research database (California requires an actual date)
- Signature of the subject and date

Three Required Statements:

- A statement that the subject has the right to give written notice to withdraw their authorization at any time, including any applicable exceptions to the right to withdraw authorization
- A statement that once the subject’s PHI has been disclosed, it is possible that the receiver may re-disclose the information
- A statement that informs the subject that they may choose to refuse to sign the authorization and this will not affect their medical treatment

General Requirements:

- The authorization must be written in plain language (approximately 8th grade level)

- A copy of the authorization form must be given to the subject

Waiver or Partial Waiver of Authorization:

For research uses and disclosures of PHI, Sterling IRB may approve a waiver or partial waiver of authorization. Partial waivers are likely to be sought to enable investigators to contact and recruit individuals as potential research subjects. The following criteria must be satisfied to grant a waiver or partial waiver of authorization:

- The use or disclosure of protected health information involves no more than minimal risk to the individuals based on at least the presence of:
 - An adequate plan to protect PHI identifiers from improper use and disclosure
 - An adequate plan to destroy PHI identifiers at the earliest opportunity consistent with the research (unless there is a health or research justification, or it is required by law)
 - Adequate written assurances against re-disclosure of the PHI (except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by regulation)
- Practicability: The research could not practicably be conducted without the Partial Waiver/ Waiver
- Access: The research could not practicably be conducted without access to and use of the PHI

B. Emergency Use of Investigational Drug or Device:

FDA and the IRB recognize that situations arise in which there could be a need to use an investigational drug, biologic, or device in a manner inconsistent with the approved protocol or by a physician who is not an investigator on the clinical study. The criteria for emergency use are defined in the Code of Federal Regulations (CFR) and must be followed. The emergency use provision in 21 CFR 56.104(c) is an exemption from prior IRB review and approval and may not be used unless all provisions of 21 CFR 56.102(d) exist. This exemption allows one use without prospective IRB review, and FDA requires that the IRB is notified within 5 working days of the emergency use of the test article. Any subsequent use requires prospective IRB review and approval.

OHRP regulations do not provide for an emergency use exception to IRB review, though OHRP regulations do allow physicians to provide emergency medical treatment to patients. In emergency use situations, OHRP regulations do not consider patients to be research subjects.

For *approval* of a test article's use in an emergency situation, a full Board review is required (expedited or subcommittee review/approval is not allowed). However, if the conditions of 21 CFR 56.102(d) are met but it is not possible to convene a quorum within the time available, the IRB Chairman or appropriate designee (a Board member with appropriate medical knowledge) may *acknowledge* notification of the emergency use.

The investigator seeking acknowledgement of emergency use of a test article should provide the IRB with a letter documenting the presence of each of the following conditions. **This notification to the IRB must occur within 5 working days of use of the test article.**

- a. a life-threatening situation exists in which no standard acceptable treatment is available
- b. the test article must be used expeditiously, meaning insufficient time is available to convene a quorum for full-Board IRB review/approval

The IRB Chairman or appropriate designee will review the investigator's letter of notification, and will only *acknowledge* emergency use of a test article if each of the following conditions exist to justify the use:

- a. a life-threatening situation exists in which no standard acceptable treatment is available
- b. the test article must be used expeditiously, meaning insufficient time is available to convene a quorum for full-Board IRB review/approval

If the IRB Chairman (or designee) confirms the presence of the necessary conditions, the IRB Chairman (or designee) will sign/send a letter to the investigator acknowledging notification of emergency use of the

test article. If the Sponsor requires a written acknowledgement from the IRB in order to approve shipment of the test article, Sterling IRB will provide the Sponsor a copy of its acknowledgement letter to the investigator.

Definitions:

Emergency Use means the use of a test article (e.g., investigational drug, biologic, or device) on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). For the purposes of 21 CFR 56.102(d), "life-threatening" includes the scope of both life-threatening diseases/conditions and severely debilitating diseases/conditions.

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

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

FDA Guidance for IDE Early/Expanded Access:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>

FDA IRB Information Sheets – Drugs and Biologics – Updated 9/98 – Guidance for Institutional Review Boards and Clinical Investigators 1998 Update:

<http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html>

There are many considerations regarding patient protections in emergency use. Please contact Sterling IRB if you are contemplating emergency use of a test article.

C. Humanitarian Use Device:

A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 people in the United States per year. To be considered for HUD status, a device sponsor must submit a humanitarian device exemption (HDE) application to the FDA. The applicant must demonstrate that no comparable devices are available for the use intended for the device in question and that the applicant device could not be brought to market without the conditions of the HDE.

Role of the IRB: This is the only situation where federal regulations require the IRB to approve and monitor an activity that is not considered research. An Application for Humanitarian Use Device is available on the Sterling website at <www.sterlingirb.com>. The application must be submitted prior to review and approval by the Board. The IRB is responsible for initial and continuing review, and Humanitarian Use Device Continuing Review forms are also available on the Sterling website.

D. Compassionate Use:

Compassionate use provisions allow access to the test article for subjects who do not meet the criteria for inclusion in an approved clinical trial. Subjects must have a serious, but not life threatening disease or condition, and the investigator must feel the deviation represents a benefit in treating and/or diagnosing their disease or condition. Prospective FDA, Sponsor and IRB approval is required prior to the use. Please contact Sterling IRB to discuss a compassionate use request.

E. Genetic Research:

Genetic research typically presents risks of social and psychological harm to participants rather than risks of physical harm. The Board will consider the following areas when reviewing a genetic testing protocol or sub-study:

- Selection of participants
- Confidentiality and privacy
- Disclosure of information
- Secure storage of data and biological samples
- Participant withdrawal (possible continued risk with long term storage of biological samples)
- Assessment of predictive value of the research study

F. Investigator Held IND/IDE:

When an investigator holds an IND/IDE, he must fulfill both the Principal Investigator and Sponsor responsibilities. Please contact Sterling IRB at 888-636-1062 for assistance.