IRB Handbook

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Summary of Changes:

Version 34.3 Changes:

- Change of Address

- Chapter 6 – CONTINUING REVIEW
  B. Final Report
    - *Clarification on when to close a study*

- Chapter 7 – REPORTABLE EVENTS

  Clarification of sponsor and investigator responsibilities regarding PHI and PII when submitting a Reportable Event.

  F. Unanticipated Problems (Other):
    - *Clarification that any audit, inspection, or inquiry by a federal agency should be reported to the IRB, as well as any written report.*

- Chapter 10 – SPECIAL TOPICS – *NEW SECTION ADDED: J. Research Involving Dietary Supplements*

Table of Contents

Table of Contents 3
Chapter 1 – INTRODUCTION 6
Chapter 2 – CATEGORIES OF RESEARCH REVIEW 7
A. Full Board Review: 7
B. Expedited Review: 7
C. Non-Human Subjects Research Determinations: 8
D. Exempt Human Subject Research: 8
Chapter 3 – PRINCIPAL INVESTIGATOR AND SPONSOR RESPONSIBILITIES 10
A. Study Conduct: 10
B. Training and Education / Investigator and Study Staff Qualifications: 10
C. Conflict of Interest: 11
D. Data Governance and Record Retention: 13
E. Audits and Inspections: 14
F. State and Local Law: 14
G. Competing Studies at Research Sites: 14
H. Summary of Requirements of the Principal Investigator: 14
J. Sponsor Responsibilities: 16
Chapter 4 – SUBMISSIONS TO THE IRB 18
A. New Study Submissions: 18
B. New Principal Investigator/Site Submission: 19
C. Amendments to Previously Approved Research: 20
D. Notification of Approvals and Acknowledgements: 22
Chapter 5 – SUBJECT RECRUITMENT 23
A. Advertisements and Recruitment Materials: 23
B. Screening Questionnaires: 25
C. Study Materials: 26

D. Generic Materials: 26
E. Referral Fees, Incentives, and Bonus Payments for Recruitment: 27
Chapter 6 – CONTINUING REVIEW 28
A. Study Status Report: (Application for Continuation) 28
B. Final Report: 29
C. Lapse in IRB Approval: 29
D. Reinstatement Requests: 30
Chapter 7 – REPORTABLE EVENTS 31
A. Protocol Deviations: 31
B. Sponsor-Granted Exceptions: 32
C. Serious Adverse Events (SAEs): 33
D. External Adverse Events (IND Safety Reports): 34
E. Unanticipated Adverse Device Effects (UADE): 34
F. Unanticipated Problems (Other): 34
G. Noncompliance: 36
Chapter 8 – INFORMED CONSENT 38
A. The Process of Consent and Assent: 38
B. Elements of Informed Consent: 38
C. Authorization to Use and Disclose Medical Information 42
D. Waiver or Alteration of Informed Consent: 43
E. Re-consenting: 44
F. End of Participation or Subject Withdrawal from a Study 44
G. Subject Compensation: 45
H. Non-English Speaking Subjects and Translations: 46
I. Short Form Consent: 46
J. Subject Contact with Sterling IRB: 47
K. Informed Consent Requirements When Determining Eligibility for Research: 47

L. Signature Requirements: 47

M. Remote and Electronic Consent (e-consent): 49

N. Charging Subjects for Study Participation ("Pay to Participate Studies") 51

Chapter 9 – VULNERABLE SUBJECTS, ADDITIONAL CONSIDERATIONS AND PROTECTIONS 52

A. Children and Minors: 52

B. Pregnant Women, Fetuses, Neonates of Uncertain Viability and Nonviable Neonates: 53

C. Prisoners: 53

D. Cognitively Impaired Persons: 53

E. Traumatized and Comatose: 54

F. Terminally Ill: 54

G. Low-Literacy and Physically Challenged Subjects (Visually Impaired/Blind and Hearing Impaired/Deaf): 54

H. Educationally Disadvantaged: 55

I. Economically Disadvantaged: 55

J. Additional Considerations – Inclusion of Women and Minorities: 55

K. Additional Protections – Students, Employees and Normal Volunteers: 56

Chapter 10 – SPECIAL TOPICS 57

A. HIPAA: 57

B. Certificates of Confidentiality (CoC): 58

C. Emergency Use of Investigational Drug or Device: 58

D. Humanitarian Use Device: 60

E. Expanded Access: 60

F. Genetic Research: 60

G. Mobile Applications: 61

H. Subject Transfers: 61

I. Return of Research Results: 61

J. Research Involving Dietary Supplements: 62

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 and 56
- Part C Division 5 of the Canadian Food and Drug Regulations and the Tri-Council Policy Statement (where applicable)
- 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.

Sterling IRB applies the requirements of the revised Common Rule to federally funded research (except for the Department of Justice) approved or determined to be exempt on or after the compliance date of the 2018 Common Rule (January 21, 2019). For federally funded research that was initiated prior to January 21, 2019, Sterling IRB will continue to apply the requirements of the pre-2018 Common Rule ('old Common Rule'). For research that is initiated on or after January 21, 2019, and is not subject to federal regulation (i.e., not federally funded and not FDA-regulated), Sterling IRB will apply all provisions of the pre-2018 Common Rule in its review of such research except for exempt determinations which will be based on the exemption categories of the revised Common Rule.

Sterling IRB is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Sterling IRB is also a member of the Consortium of Independent Review Boards (CIRB), a non-profit organization of independent institutional review boards committed to the ethical review of clinical research and the protection of human research participants.

For questions, comments, or suggestions regarding the review of research at Sterling IRB, contact us at (770) 690-9491, toll-free at 1 (888) 636-1062. Please also visit the Sterling IRB website at www.sterlingirb.com for additional information regarding Sterling IRB, to access and learn more about the SilverLink web portal, and for additional resources regarding the research process. SilverLink is Sterling IRB's secure web-based portal. Users can retrieve documents from Sterling IRB and submit materials for Sterling IRB review via dynamic smart forms.

This handbook outlines the responsibilities of the Principal Investigator and Sponsor/CRO and should be read by the key personnel on the research team. The IRB is available as a resource to assist investigative sites in any matters that involve research participants (e.g., complaints, concerns). 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.

Chapter 2 – 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 and that are not eligible for expedited review require review by the full Board at a convened meeting. Sterling IRB typically convenes daily panels (Monday – Friday). For research conducted in Canada or in both the US and Canada, the Sterling IRB North American panel serves as a duly convened IRB/REB for review of research in both the United States and Canada[1]. The IRB's current membership roster is available on the Sterling IRB website at https://sterlingirb.com/board-rosters/ or in SilverLink under Useful Links. Any changes to the roster are updated on the website and in SilverLink.

Sterling IRB typically uses a primary reviewer system for full Board reviews, with submission application materials typically sent to the Board at least 3 business days prior to a meeting. When a primary reviewer is used, their assessment guides discussion of the project under review and the Board determines whether the project meets the criteria for approval and whether revisions to the protocol or informed consent are needed. The primary reviewer is selected by the Chairperson and/or designee based on the Board member's expertise.

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 provided within 2 business days.

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, a statement of the reason for the Board's decision, and will give the Principal Investigator an opportunity to respond in person or in writing. The Principal Investigator may submit an appeal of the Board's determination(s). The appeal must be in writing, addressed to the Board Chairperson, 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.

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.

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

[1] Sterling IRB does not provide oversight for research in Alberta, Saskatchewan, and Newfoundland and Labrador. In Québec, Sterling IRB only reviews research involving adults with capacity to consent.

procedure for minor changes in previously approved research during the period of review for which approval is authorized, and for initial review of studies in permissible categories as detailed in the Federal Register.

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

C. Non-Human Subjects Research Determinations:

Following receipt of submission materials, Sterling IRB will determine whether the proposed activity meets the regulatory definition of human subjects research as defined by FDA [21 CFR 50.3(c) and (g); 21 CFR 56.102(c) and (e); 21 CFR 312.3(b); 21 CFR 812.3(h) and (p)] and DHHS [45 CFR 46.102(e) and (l)]. A study must involve both "human subjects" and "research" according to the applicable regulation(s) to be considered human subjects research. If a study is subject to both FDA and DHHS regulations and constitutes human subjects research under only one set of regulations, the study must still receive IRB review pursuant to the regulations that classify the study as human subjects research. If the activity is determined to be non-human subjects research, the Sponsor (and investigator, if applicable) will be notified in writing within 48 hours of the determination being made. The Exemption or Non-Human Subjects Research Determination Request form should be submitted to request a Non-Human Subjects Research determination from the IRB. Scholarly and journalistic activities and government functions with separately mandated protections are not considered research.

D. 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 46.104) (21 CFR 56.104). The Chairperson 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. The Exemption or Non-Human Subjects Research Determination Request form should be submitted to request an exemption determination from the IRB.

To aid those who need to decide if an activity is research involving human subjects that must be reviewed by an institutional review board (IRB), the U.S. Department of Health & Human Services has made decision charts available here: https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts-2018/index.html

Studies that meet the criteria for an exemption do not undergo continuing review.

During the course of a study determined to meet the criteria for exemption or determined to be non-human subjects research, changes to the study may be necessary. Sterling IRB does not review amendments for exempt or non-human subjects research; however, if the revision impacts the risk to participants, increases the research to greater than minimal risk, and/or affects the criteria for exemption under which it was determined, IRB review may be required and a New Study Submission Application should be submitted. If your study has received an exemption or non-human subjects research determination from the IRB, please contact the IRB if you are planning to:

- Add procedures that could affect risks to participants; or
- Add procedures that do not fit within the exemption categories; or
- Add new types of participants to your study that include vulnerable populations (e.g., adding children, individuals with cognitive impairments, prisoners, etc.)
- Change of Principal Investigator
- Examples of changes that would likely require IRB review include, but are not limited to, the following: Removal of the consent process, or use of deception or incomplete disclosure.
- Significant changes to the recruitment procedures.
- Adding sensitive questions to a survey or interview process (e.g. questions regarding illegal activities; traumatic events such as childhood, sexual, or domestic abuse; suicide; or other probing questions that

could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation).
- Collection of new or additional identifiable information.
- Changes to the data storage plan which may affect confidentiality.

Chapter 3 – PRINCIPAL INVESTIGATOR AND SPONSOR 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 their 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 has the resources necessary to protect human participants, including:

- Sufficient time to conduct and complete the research
- Adequate number of qualified staff
- Adequate facilities
- Availability of medical or psychological resources that participants may need as a consequence of the research
- A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions
- 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, in the case of an investigator-blinded trial, should ensure that the identification code is broken only in accordance with the protocol. In the case of an emergency, to protect patient safety, the investigator should be prepared and capable from the start of the trial to perform unblinding without undue delay and hinderance. If the trial is blinded, the investigator should promptly (within 30 days) document and explain to the sponsor any premature unblinding (e.g. accidental unblinding, emergency unblinding to protect trial participant, unblinding due to an SAE) of the investigational product. The Principal Investigator is also responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor. In generating, recording, and reporting trial data, the investigator should ensure the integrity of the data under their responsibility, irrespective of the media used. The Principal Investigator agrees to abide by the Investigator Compliance Agreement as stated in the Submission Application for the Investigator/Site.

Furthermore, if applicable, the Principal Investigator and Sponsor are required to ensure the study does not begin until the IND or IDE is in effect. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

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

Training and education in the ethical conduct of human research is essential in protecting the rights and welfare of humans participating in research studies. 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. Key study personnel include the principal investigator, the sub-investigator(s), and the study coordinator(s). This training includes, but is not limited to, the following topics:

- Good Clinical Practice (GCP)
- The Health Insurance Portability and Accountability Act of 1996 (HIPAA Privacy Rule)
- The Belmont Report
- FDA and DHHS regulations
- Tri-Council Policy Statement (TCPS 2), where applicable
- Health Canada Regulations, where applicable

Sterling IRB accepts training completed in a variety of formats and from a variety of sources. The most common training formats include online training modules, live lectures and seminars, self-study texts that provide CEU and CME credit, and college courses. The various sources through which one may obtain training include government entities, professional organizations, non-profit institutions, and commercial businesses. Sterling IRB is pleased to offer Collaborative Institutional Training Initiative (CITI) educational resources to participating Investigators and their staff. For additional information on this program, please contact us at citiadmin@sterlingirb.com. Also see the Sterling IRB website (www.sterlingirb.com) for additional training resources.

For investigators affiliated with an institution, your institution may have additional training requirements. Please check with your institutional official to verify the training requirements for which you and your study personnel are responsible.

The Principal Investigator is responsible for providing evidence of his or her qualifications through a current curriculum vitae or other relevant documentation requested by the Sponsor, the IRB, or the regulatory authority. If applicable, the principal investigator's medical license number is required at the time of initial submission to the IRB. Sterling IRB will verify that the investigator holds an active medical license. The PI is also responsible for promptly notifying Sterling IRB of any pending or ongoing legal, regulatory, or professional actions or restrictions related to the practice of medicine or research at the site(s). Please note, Sterling IRB is not responsible for monitoring the expiration date of an investigator's medical license. Information related to sub-investigators/research staff may be requested by Sterling IRB on a case-by-case basis.

The PI may delegate trial-specific activities to other persons or parties. However, the PI retains the ultimate responsibility and maintains appropriate supervision of all personnel to ensure the rights, safety, and well-being of the trail participants and data reliability. The investigator should ensure that personnel are appropriately qualified and supervised and are adequately informed about the protocol, the investigational product(s) and their assigned trial activities. Trial-related training should correspond to what is necessary to enable personnel to fulfil their delegated trial activities that go beyond their usual training and experience.

The PI is responsible for maintaining a list of appropriately qualified personnel to whom they have delegated significant trial-related duties. While Sterling IRB does not require the review and approval of additional study personnel, Sterling IRB must be promptly notified of any pending or ongoing legal, regulatory, or professional actions or restrictions related to the practice of medicine or research at the site(s), and any relevant conflicts of interest. In addition, research personnel must comply with the requirements and determinations of Sterling IRB.

If a principal investigator will be unable to maintain primary oversight during a leave of absence, the investigator should delegate responsibility for study oversight to an appropriately qualified research staff person, typically a sub-investigator. Planned leave of more than 3 months requires a change in principal investigator and must be reviewed and approved by Sterling IRB prior to the absence. Planned leave of 3 months or less is generally acceptable with submission of a management plan detailing how study oversight will continue uninterrupted. Any revisions to the management plan during the course of the leave should be submitted to the IRB for review. For unplanned PI leave of absence of any length, the site should inform Sterling IRB as soon as possible so that either a management plan can be developed or a change in investigator initiated.

C. 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.

Sterling IRB requires disclosure of the following financial interests of the investigator, study staff and their spouse and dependent children):

- Financial arrangement entered into between the sponsor of a study and the investigator whereby the value of the compensation for conducting the study could be influenced by its outcome. For example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to the sales of the product, such as royalty interest.
- For publicly traded entities: the value of any remuneration received from the entity in the past 12 months *plus* the current value of any equity interest in the entity exceeds $5,000*, *and* this financial interest reasonably appears to be related to the investigator's responsibilities for a study. For purposes of this definition, "remuneration" includes salary and any other payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship) and "equity interest" includes any stock, stock option, or other ownership interest as determined through reference to public prices or other measures of fair market value.
- For non-publicly traded entities: the aggregate value of any remuneration received from the entity in the past 12 months exceeds $5,000* *or* any equity interest is held (e.g., stock, stock option, or other ownership interest) *and* this financial interest reasonably appears to be related to the investigator's responsibilities for a study.
- Any significant equity interest in a study's sponsor (i.e., any ownership interest, stock options, or other financial interest) whose value cannot be readily determined through reference to public prices. This generally applies to interests in a sponsor that is not a publicly traded entity.
- Intellectual property or other proprietary rights and interest (e.g. patents, copyrights, trademarks, licensing agreements) that reasonably appear to be related to the investigator's responsibilities for a study (e.g. rights/interest in the tested product); includes receipt of income related to such rights and interests.
- Reimbursed or sponsored travel (i.e., that which is paid on behalf of the investigator and not reimbursed to the investigator so that the exact monetary value may not be readily available) related to the investigator's responsibilities for a study; provided, however, that this disclosure does not apply to travel that is reimbursed or sponsored by a Federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C.1001(a), an academic teaching hospital, or a research institute that is affiliated with an institution of higher education.
- An ownership interest, stock options or other financial interest in a study that is valued at $10,000 or more* or 5 % or greater* ownership.
- Receipt of significant payments of other sorts with a cumulative monetary value of $25,000 or more made by a study's sponsor to the investigator or their institution to support activities of the investigator exclusive of the costs of conducting clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria).
- An executive, director, or employee of the sponsor of a study.
  ** This threshold limit applies to the aggregated financial interests of the investigator or study staff plus their spouse and dependent children.*

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. The report should be accompanied by a plan for managing and minimizing the disclosed interests. Some possible actions that can be taken to manage potential conflicts include:

- Public disclosure of the significant conflict of interest
- Monitoring of the research by independent reviewers
- Modification of the research plan
- Divestiture of significant financial interests

Sterling IRB has the final authority to decide whether the conflict and its management, if any, allows the research to be approved. Please note that failure to disclose possible conflicts of interest and/or failure to adequately manage the conflict is considered non-compliance with the requirements of the IRB.

For additional information, refer to HHS's guidance Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection or the FDA guidance document, Financial Disclosure by Clinical Investigators.

In compliance with the Tri-Council Policy Statement, Sterling IRB requires that all Canadian sites provide their clinical trial budget for review. The budget will be reviewed to ensure that conflicts of interest are identified and minimized or otherwise managed. In general, payments for clinical trial procedures should be no greater than the usual amounts charged by health care providers for the provision of comparable services.

D. Data Governance and Record Retention:

Data Acquisition Tool: A paper or electronic tool designed to collect data and associated metadata from a data originator in a clinical trial according to the protocol and to report the data to the sponsor.

The data originator may be a human (e.g., the participant or trial staff), a machine (e.g., wearables and sensors) or a computer system from which the electronic transfer of data from one system to another has been undertaken (e.g., extraction of data from an electronic health record or laboratory system).

Metadata: The contextual information required to understand a given data element. Metadata is structured information that describes, explains or otherwise makes it easier to retrieve, use or manage data. For the purpose of research, relevant metadata are those needed to allow the appropriate evaluation of the trial conduct.

Source Records: original documents or data (that include relevant metadata) or certified copies of the original documents or data, irrespective of the media used. This may include trial participants' medical/health records/notes/charts; data provided/entered by trial participants (e.g., electronic patient-reported outcomes (epros); healthcare providers' records from pharmacies, laboratories, and other facilities involved in the clinical trial; and data from automated instruments, such as wearables and sensors.

Investigators and/or sponsors should ensure the appropriate management of data integrity, traceability and security, per the ICH GCP E6(R3) guidelines, to allow for accurate reporting, verification, and interpretation of the clinical trial-related information.

The quality and amount of information generated in a clinical trial should be sufficient to address trial objectives, provide confidence in the trial's results and support good decision-making. The systems and processes that help ensure this quality should be designed and implemented in a way that is proportionate to the risks to participants and the reliability of trial results.

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 for maintaining complete and accurate records for the following:

- Source records for each subject. Source records should be attributable, legible, contemporaneous, original, accurate, and complete.
- 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.

In accordance with regulatory requirements, Sterling IRB will retain study records for at least 3 years after the last site under Sterling IRB oversight has completed the study.

All electronic records are automatically stored and backed-up for the full retention period. Once the retention period has been met, an email notification will be sent to the individual(s) that were last known study contact(s). The notification will instruct the study contact(s) to retrieve any needed documentation within 30 days. After the 30-day period, all documentation will be purged from Sterling's electronic systems.

E. Audits and Inspections:

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

Sponsors and investigators are required to immediately notify Sterling IRB of any audit resulting in the Sponsor terminating or suspending the site. The notification should be submitted via the Reportable Events Form and include the reason for the suspension or termination as well as any applicable corrective action plan(s). Sterling IRB will review the information provided and take appropriate action (e.g., suspend or terminate IRB review). Sterling IRB reports all suspension and terminations of IRB review to the proper regulatory agencies.

Sponsors and/or investigators are required to report a regulatory agency audit or any enforcement action (including Form FDA 483, FDA Warning Letter, A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain) within 10 business days.

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.

Sterling IRB randomly audits active investigative sites 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.

F. State and Local Law:

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

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.

G. Competing Studies at Research Sites:

In the event that a potential research participant is eligible for multiple studies being conducted at the research site, it is the Principal Investigator's responsibility to ensure the site maintains a procedure to address how the PI will determine which study is most appropriate for the potential participant.

H. 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 within 10 business days.

- **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. Please note, Sterling IRB issues site-specific consent form(s) containing approved site-specific information to each site. The site must use the IRB approved/issued consent form(s) for consenting participants.

- **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 the Modifications and Amendments Submission Form.

- **Reportable Events:** Protocol Deviations, Serious Adverse Events, External Adverse Events ("IND Safety Reports"), Sponsor-Granted Exceptions and Other Unanticipated Problems, as described in Chapter 7.

- **Continuing Review Reports:** At a minimum, all reports should 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.

  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.

- **Study 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 Study 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 Study 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 Study Status Report must be submitted to ensure proper closeout. This report should include the date that the final subject completed the study. A Study Status Report should also be filed in the event of suspension, cancellation or termination of a study.

- *Sterling IRB also makes available a summary sheet entitled "Events Reportable to the IRB" on its website at www.sterlingirb.com.*

I. Institutional Relationships with Sterling IRB:

Sterling IRB is a participating member of SMART IRB. Through a flexible master IRB reliance agreement, standard operating procedures, and complementary tools and resources, SMART IRB is designed to harmonize and streamline the IRB review process for multisite studies, while ensuring a high level of protection for research participants. Sterling IRB is looking forward to working with Participating Investigators and Institutions of the SMART IRB network.

Sterling IRB is registered with the Department of Health and Human Services (DHHS) as IRB00001790 and complies with all federal regulations pertaining to the protection of human research participants. As an Independent Review Board, Sterling IRB can serve as the IRB of record for institutions such as medical centers, academic institutions, and community hospitals if one of the following conditions is met:

- There is no local IRB with jurisdiction.
- The local IRB has jurisdiction but defers it to Sterling IRB in writing.

Institutions who are requesting that Sterling serve as the IRB of record for a study that would normally fall under local IRB jurisdiction may submit the IRB Jurisdiction Form located in the Forms for Institutions section of the Forms page. When ceding review to Sterling IRB, Sterling IRB will serve as the IRB of record and Sterling IRB policies will take precedence.

If an institution is conducting research under a Federalwide Assurance (FWA) and plans to use the services of Sterling IRB, it must complete an IRB Authorization Agreement (available within the Forms for Institutions section of the Forms page), and may need to update its FWA if Sterling is not already included as a designated IRB. The institution remains responsible for ensuring compliance with Sterling IRB's determinations and with the terms of its OHRP-approved FWA. The Institution will notify Sterling IRB promptly in writing of any suspension, restriction, termination, or expiration of its FWA. Please note that Sterling IRB does not require additional reliance/authorization agreements from participating SMART IRB institutions.

To learn more about Sterling's partnerships with institutions, please download our Institution Start-Up Package or call 1-888-636-1062 or email us.

Investigators who conduct research at institutions and are applying to Sterling should be aware of any obligations that they may have to use the institution's IRB. It is also the Principal Investigator's responsibility to ensure their local IRB requirements are met prior to ceding review to Sterling IRB.

J. Sponsor Responsibilities:

Sponsors are responsible for selecting qualified investigators with appropriate education, training and experience to conduct the clinical trials.

The Sponsor must ensure the site has adequate resources and facilities (e.g., emergency equipment and personnel) to properly conduct the study. The sponsor must monitor the site(s) to ensure proper conduct of the study and compliance with Sponsor and IRB requirements. The Sponsor is also responsible for promptly (within 10 days) communicating to the IRB any finding(s) that may impact the safety of research subjects or influence the conduct of the research study as well as any terminations or suspensions of the Principal Investigator due to noncompliance or safety issues.

When appropriate, Sponsors should ensure contracts with the investigator (or the investigator's institution) indicate who will provide care and who is responsible to pay for research related injuries. Sponsors should also have a process to confirm the terms specified in the contract are consistent with the consent document.

The Sponsor must ensure the investigational product is used in accordance with the approved protocol and manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP).

The Sponsor is responsible for the prompt distribution of approved study materials to all approved study sites. The Sponsor must also ensure the site is properly trained on all approved study materials. As a courtesy, study documents may be available within the Study Attachments section of Silverlink. These documents do not preclude the Sponsor from their responsibility to distribute study materials. The template version of the ICF located within Study Attachments should not be used for consenting participants.

For investigator sponsored studies, the sponsor-investigator assumes the responsibilities applicable to an Investigator and a Sponsor.

If a study under Sterling IRB oversight will be registered on ClinicalTrials.gov, the following information should be listed regarding human subjects review:

Board Approval Number: IRB ID #
Board Name: Sterling Institutional Review Board
Board Affiliation: Sterling Institutional Review Board
Board Contact:

Phone: 888-636-1062
Email: info@sterlingirb.com
Address: 6300 Powers Ferry Road, Suite 600 – 351, Atlanta, Georgia 30339

See the ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies document for additional information. https://clinicaltrials.gov/submit-studies/prs-help

Chapter 4 – SUBMISSIONS TO THE IRB

A. New Study Submissions:

Sponsors/CROs may submit a research study for review and approval prior to submission of a principal investigator. However, please note that each Principal Investigator that will be under Sterling IRB oversight must also receive Sterling IRB review and approval prior to conducting this study.

Principal Investigators are required to submit the Submission Application for the Investigator/Site (and attachments). Principal Investigators who are submitting an Investigator-Initiated study must also submit a New Study Submission Application.

A new study should be submitted to Sterling IRB via the New Study Submission Application along with the following attachments:

- Final Protocol
- Sub-Study materials and documentation (if applicable)
- Consent Document(s)
- Study-wide Recruitment Materials and Study Materials (questionnaires, diaries, etc.) *Note:* Any commercially available validated instruments that are cited in the protocol and will be used **without modification** will not be listed on the approval letter. Approval of the protocol extends to the uses of such industry standard forms.
- Product information (e.g., investigator's brochure, package insert, device instructions for use, device manual, manual of procedures, lab manual, pharmacist's manual, certificate of analysis (COA)), if applicable[2]

Transfer of IRB Oversight:

Sterling IRB may also review requests to transfer IRB oversight of a study from another IRB to Sterling IRB. To protect study participants and reduce the disruption of study activities, IRB oversight should be transferred such that there is no lapse in IRB oversight. Studies incoming to Sterling IRB via transfer from another IRB will be reviewed *de novo.* In addition to the standard submission materials solicited from Sponsors and Principal Investigators seeking approval of new studies, the following documentation must also be submitted by Sponsors and Principal Investigators seeking to transfer IRB oversight of an ongoing study:

- From the Sponsor:
  - Information regarding the previous IRB
  - Number of Principal Investigators transferring to Sterling IRB
  - Reason for the transfer
  - Date of initial approval and current study expiration date
  - Continuing review documentation from the previous IRB
  - Study status and enrollment information
- From the Principal Investigator:
  - Information regarding the previous IRB
  - Reason for the transfer
  - Date of initial approval and current study expiration date
  - Continuing review documentation from the previous IRB
  - Study status and enrollment information

If the study being submitted for review was previously disapproved by another IRB, the reason for disapproval will need to be submitted in conjunction with the New Study Submission Application.

[2] Any document that contains information regarding study activities or the appropriate use of the study product should be submitted to the IRB.

B. New Principal Investigator/Site Submission:

Each Principal Investigator that will be under the oversight of Sterling IRB must be reviewed by Sterling IRB and receive approval prior to conducting the applicable study. Principal Investigators are required to submit the Submission Application for the Investigator/Site (and attachments).

The Submission Application for the Investigator/Site should include the following attachments, if applicable:

- A copy of the PI's signed and dated CV (unless a current CV has been submitted to Sterling IRB within the last two years)
- If the PI's medical license(s) cannot be verified online, please attach a copy of the medical license(s)
- PI's DEA Registration certificate (only required if the study involves controlled substances)
- A copy of the Sterling IRB approved informed consent form(s) with the tracked changes that are requested by the site. All consent changes will need Sponsor and IRB approval, unless otherwise stated by the Sponsor. By using the consent form template, you can be confident that you are starting with the most recent IRB and sponsor-approved language, thereby ensuring accurate version control, while saving you, and Sterling IRB, time and effort. Changes that are not explicitly tracked within the consent form will not be incorporated/reviewed.

  Please note, a tracked consent form should not be submitted if the only changes are inserting the Principal Investigator's information into the merge fields of the template consent form.

- A payment schedule specifying the number of visits and payment for each visit
- Site-specific recruitment/study materials

Site-specific information included in the Submission Application for the Investigator/Site will be used by Sterling IRB to generate your site-specific consent form(s). Sterling IRB will generate a consent form for the PI by incorporating any institutionally required language that has been provided to the IRB and the site-specific information such as payment information, etc. into the previously approved consent form template (i.e. merge fields).

Site-specific information which must be provided on the Sterling IRB Submission Application for the Investigator/Site form includes:

- All telephone numbers for the consent form. A 24-hour number for emergencies is required for all greater than minimal risk studies.
- If participants will be paid, a payment schedule specifying the number of visits and payment for each visit. The exact wording detailing this information, including correct payment totals, must be submitted to Sterling IRB for review. Please note, it is the responsibility of the applicant to include correct payment information within the submission. Sponsor approval of the information may be required.

Sterling IRB requires all sites that fall under the Section 3 guidance of the 1572 to be submitted for review/approval. Section 3 is intended to identify facilities where study activities will be conducted and clinical data will be generated or collected. This includes facilities where subjects will be seen and study procedures performed. For example, this might include locations such as health care facilities where the test article will be administered, or where physical exams will be performed. Facilities where other important clinical investigation functions are performed may also be identified in Section 3. For example, a research laboratory where the test article is prepared, a special storage facility where the test article will be kept, or a location where tissue specimens are collected should be listed in this section. Only the primary site location must be listed on the consent form(s). Therefore, a site may have supplemental sites that are not listed on the consent form(s).

Institutions who are requesting that Sterling serve as the IRB of record for a study that would normally fall under local IRB jurisdiction may submit the IRB Jurisdiction Form located in the Forms for

Institutions section of the Forms page. Please refer to Chapter 3 – PRINCIPAL INVESTIGATOR AND SPONSOR RESPONSIBILITIES, section I. Institutional Relationships with Sterling IRB for further information.

Sterling IRB may also review requests to transfer IRB oversight of a study from another IRB to Sterling IRB. Please refer to section A. New Study Submissions for further information.

C. Amendments to Previously Approved Research:

Any change to previously approved research must be reviewed and approved by the IRB prior to implementation, except changes made to eliminate immediate safety hazards to participants, which must be reported to the IRB within 10 business days.

Protocol Amendments:

Protocol amendments should be submitted to Sterling IRB via the Modifications and Amendments Submission Form, along with the following attachments:

- Copy of clean Protocol
- Copy of tracked change version of protocol
- Copy of Sterling IRB approved informed consent template with tracked changes, if applicable
- 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

If an amendment requires changes to the informed consent document, please follow the directions listed below in the “Revised Informed Consent Form(s)” section.

Please note, Sterling IRB does not stamp and/or distribute certain documents (i.e., protocols, FDA correspondence, etc.) to sites as it ensures that sites have been properly trained on the procedures and risks of the study per the Sponsor’s SOPs. While documents may be available for reference in the “Study Attachments” section of SilverLink, this does not supplant the Sponsor/CRO from distributing documents to sites.

Revised Informed Consent Form(s):

Revisions to the informed consent form(s) should be submitted via the Modifications and Amendments Submission Form. All requested changes must be tracked in the most current approved version of the ICF. Revisions made on the current approved version may significantly reduce the processing time and result in more rapid receipt of approval documents. If you need to request a Word version of the ICF, please email info@sterlingirb.com or check with your Sponsor/CRO.

Sterling IRB creates the consent templates with “merge fields” for the protocol title, protocol number, site specific information (PI address, phone numbers, compensation), and the Sponsor name. These fields will be populated when you receive the final documents. In addition, Sterling IRB will generate the site-specific consent form for the PI by incorporating any institutionally required language that has been provided to the IRB.

Please note, Sterling IRB generally uses Sponsor/CRO ICF version dates and/or numbers as submitted. If an ICF is submitted with no versioning information in the footer, Sterling typically recommends that an ICF version date is incorporated to align with the current protocol date. Sterling IRB does not routinely update these version dates and/or numbers unless the submitted consent form indicates that this information should be updated. Following review and approval of the consent form, Sterling IRB will include the IRB approval date of the ICF in the footer of the document via the “Date Approved by Sterling IRB”. This date will correspond with the approval date on the issued approval document.

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

After review and approval, Sterling IRB issues site-specific consent form(s) containing approved site-specific information to each site. Your site must use the IRB approved/issued consent form(s) for consenting participants. Instructions to locate IRB-approved site-specific consent form(s) are included within the Documents Available email sent to each applicable site as well as in section D. Notification of Approvals and Acknowledgements below.

Changes to Study Product Information (e.g., investigator's brochure, package insert, device instructions for use):

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 via the Modifications and Amendments Submission Form. 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. Changes to the Investigator's Brochure will be reviewed and acknowledged.

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:

- A Submission Application for the Investigator/Site is required to request a change of Principal Investigator.
- CV of the new Principal Investigator (*unless the CV has been submitted to Sterling IRB within the last 2 years)*
- Copy of the new Principal Investigator's DEA registration (only required if the study involves controlled substances)

Change in Site Information:

When there is a change in site information (e.g., change in site location, addition of site locations, change in subject compensation, or change in site name or telephone number) for an already approved Principal Investigator, the following is required to be submitted to Sterling IRB:

- The Modifications and Amendments Submission Form

Planned increase in study enrollment:

When there is a planned increase in study-wide enrollment by over 10% (i.e., when enrollment will exceed the number stated in the current IRB approved protocol by over 10%), the following is required to be submitted to Sterling IRB:

- Modification and Amendments Submission Form
- Revised protocol or administrative letter to the protocol
- Revised informed consent form (if applicable)

Change in planned enrollment of vulnerable populations:

When there is a change in planned enrollment of vulnerable populations, the following is required to be submitted to Sterling IRB:

- Modification and Amendments Submission Form (please include a description of additional safeguards that will be used to protect the rights and welfare of each vulnerable population)

D. Notification of Approvals and Acknowledgements:

All notifications from Sterling IRB are sent via email. The "Documents Available" SilverLink notification will include direct links to the associated event, the approval or acknowledgement letter, and the attachments. It is the responsibility of the Sponsor/CRO and Principal Investigator to ensure the contact information on file with Sterling IRB is accurate and complete.

Please note, the Sponsor email notification will include links to template consent form(s). The template consent form(s) will be watermarked with "TEMPLATE", unless an alternative is agreed upon by the submitter and IRB. Sterling IRB issues the site-specific consent form containing approved site-specific information to each approved PI/site. The watermarked "TEMPLATE" consent form(s) should not be distributed or used to consent participants. The most current, approved site-specific consent form(s), may be found within Silverlink using the following steps:

1. From the home page, locate the "My Studies" section.
2. Select the applicable site/IRB ID number.
3. Scroll to the bottom of the site-page and locate the "Events" section. Please note that if you select the MASTER page, you will only find the template ICF.
4. The site-specific consent form(s) can be found within the New Study or PI/Site Submission Event as an attachment. If the consent form(s) has been revised, the ICF may be found within the applicable Modifications & Amendments event as an attachment.
5. If you require additional assistance, you may contact info@sterlingirb.com.

The following details the notification and acknowledgement timelines:

- Full Board Review of a New Study or Proposed Modification/Amendment to a Previously Approved 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: 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: Recruitment materials provided with the original submission will be reviewed with initial review. Recruitment materials submitted after that time will typically be reviewed by expedited review and you can expect approval documents to be posted to SilverLink within 2 business days of approval.
- Serious Adverse Events: Acknowledgements will usually be sent within 1 week of Sterling IRB's review.
- Significant Protocol Deviations: Acknowledgements will usually be sent within 1 week of Sterling IRB's review.
- Sponsor-Granted Exceptions: Approval documents will usually be sent within 5 business days of review.
- 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 semi-monthly.
- Study Status Report: Approval documents will usually be sent within 2 business days of Sterling IRB's review.
- Site Final Report: Approval documents will usually be sent within 2 business days of Sterling IRB's review.

Chapter 5 – SUBJECT RECRUITMENT

A. Advertisements and Recruitment Materials:

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.

Advertisements and recruitment materials should be limited to the information prospective participants needs to determine their eligibility and interest, such as:

- The name and address of the Principal Investigator or the research site
- The purpose of the research
- In summary form, the criteria that will be used to determine eligibility for the study
- A brief list of benefits to participants, if any, should be included but not guaranteed
- The time or other commitment required of the participants
- The location of the research and the person or office to contact for further information.

Sterling IRB requires that advertisements and recruitment materials include:

- A statement that the information provided pertains to a research study/clinical trial/clinical study (or equivalent)
- Language appropriate for the subject population (e.g., For pediatric studies, advertisements should be directed at adults and include a definition of the word "placebo")

In addition, Sterling IRB requires that advertisements and recruitment materials do NOT:

- State or imply a certainty of favorable outcome beyond what is outlined in the consent document and the protocol
- Emphasize (e.g., by such means as larger or bold type) compensation. References to compensation should be balanced by a description of the subject's responsibilities during the study (e.g. the number of study visits that are required for participation)
- 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)
- 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 misleading mottos or inducing or enticing terms such as "state of the art," "cutting edge," "breaking technology," or "improved."
- Make claims, explicitly or implicitly, that the test article is known to be equivalent/superior to any other drug, biologic, or device
- Make claims, explicitly or implicitly, that the test article is safe/effective for the purpose under investigation
- Make claims, explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling
- Promise "free treatment," when the intent is only to say subjects will not be charged for taking part in the research
- Use the terms "new treatment", "new medication" or "new drug" for recruitment into investigational drug, biologic or device studies without explaining that the test article is investigational
- Include coercive language, tone, or exculpatory language

- Refer to the FDA or IRB in any other capacity than what is stated in the consent

The Board may request submission of documents that require potential subjects to sign, such as a code of conduct/house rules, meal plans, floor plans, even if it does not include specific study information. Any reference to a specific study will be considered part of the recruitment process and is subject to IRB review and approval.

For print advertisements, a copy of the print ad should be submitted in the format that it will appear, so that Sterling IRB can review the layout of the advertisement as well as the text. If advertisement recruitment materials are being submitted 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 the Principal Investigator's responsibility to ensure that the submission includes any web content which requires IRB review. Print advertisements that are approved by the IRB may be used as website recruitment advertisements without further IRB approval, if they are not modified in any way.

Communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), news stories, and publicity intended for other audiences, such as financial page advertisements directed toward prospective investors, do not require 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 for review and approval prior to use where the opportunity to add additional descriptive information is not prevented by the system format.

It is the Principal Investigator's 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.

The Sponsor or site may prepare a package of recruitment materials/advertisements for the site 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 (if already approved by the IRB), 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 as the IRB may request edits to meet advertisement requirements. All recruitment media (e.g., MP3s for radio ads, MP4s/Vimeo links/YouTube links, etc. for television ads) must be approved before advertising begins. In accordance with 45 CFR 46.115 and 21 CFR 56.115, Sterling IRB must retain copies of materials that have been reviewed. Therefore, recruitment media should be provided to Sterling IRB in an electronic format that can be saved, as hyperlinks may be modified or removed over time.

Recruitment materials/advertisements provided with the original submission will be reviewed with initial review. Sterling IRB will notify the Principal Investigator or designee 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. Please note, it is not a requirement that the stamped copy is used for dissemination/publication. Therefore, requests to re-issue a document with the "Approved" stamp moved to a different area in the document will not be fulfilled. However, no alterations to the disseminated/published copy should be made without prior IRB review and approval.

Recruitment materials/advertisements submitted after the Investigator's initial review must be accompanied by the 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.

All recruitment materials must be reviewed in their final format prior to use. 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.

For research subject to the Department of Veterans Affairs (VA) requirements, VA investigators are responsible for the following during the recruitment process:

- Making initial contact with the prospective subject in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research (e.g., if the prospective subject has diabetes, the subject may indicate a desire to be notified of any diabetes-related research studies).
    - The initial contact must provide a telephone number or other means that the prospective subject can use to verify the study constitutes VA research.
- Ensuring that all original or digitalized signed and dated informed consent documents are maintained in the investigator's research files, readily retrievable, and secure.
- Creating or updating a VA health record and creating a progress note for all research subjects (Veterans or non-Veterans) who receive research procedures or interventions as inpatients or outpatients at VA medical facilities that are either used in or may impact the medical care of the research subject at a VA medical facility or at facilities contracted by VA to provide services to Veterans (e.g., Community-Based Outpatient Clinics or community living centers). Informed consent documents are not required to be in the health record.

B. Screening Questionnaires:

Sterling IRB requires that a screening questionnaire includes the following information:

- The purpose of the questionnaire
- For telephone screenings, the prospective subject must provide their permission for the screening to proceed and be informed if any sensitive information will be collected
- 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 they do 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 latter case, the prospective subject must give their permission for the information to be stored)
- For telephone screenings, the prospective subject must be told that they do not have to answer any questions they do not want to respond to and may choose to end the screening at any time.

Below is suggested screening questionnaire 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 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 screening at any time. This survey 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 screening ended
If “yes”, proceed to next question:

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

If answer is “no”, person should be thanked, and screening 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; K. 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. Note: See Chapter 10 – SPECIAL TOPICS, A. HIPAA, for additional information:

If Protected Health Information (PHI) is to be recorded into a database, the Principal Investigator will need to submit an Application for Partial Waiver of Authorization - For Recruitment Purposes. The Application should be submitted along with the screening questionnaire for approval.

C. Study Materials:

All materials that will be used as part of a study must be reviewed and approved by the IRB prior to use. This includes subject-facing materials, participant materials and retention materials. 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 are considered an amendment and should be submitted via the Modifications and Amendments Submission Form. *Note:* Any commercially available validated instruments that are cited in the protocol and will be used **without modification** do not need to be submitted separately. Approval of the protocol extends to the uses of such industry standard forms.

Site-specific information (such as site name, address, and contact information) may be inserted into approved study materials without further IRB review, taking care not to alter the layout, type font, or size of the approved material. Any additional modifications must be submitted to the IRB for review and approval.

D. Generic Materials:

“Generic” materials are items that an investigator wishes to use outside of the context of a specific protocol, or materials that a Sponsor/CRO/Site Management Organization (SMO) would like to use that do not identify any one specific investigator and/or protocol, and do not include research procedures.

Common types of generic materials include:

- Generic Advertising, including Brochures, audio-visual materials, Web Content
- Generic Pre-Study Screening Consent Forms
- Generic Telephone Screening Scripts
- Generic Consent for Photography

Consent forms, participant letters, or other information used after recruitment or consent may not be considered generic and should be submitted for review on a study-by-study basis. All study related documents should be reviewed by the overseeing IRB in the context of the protocol. Any document that

references a specific study is subject to IRB review and approval. Documents that include placeholders for protocol information cannot be reviewed via generic review.

Generic materials should not include specific information regarding payment to subjects as the suitability of a particular payment plan is protocol specific. A general statement such as “participants will be paid for their participation” is recommended instead.

Study sites that require potential subjects to sign a code of conduct or similar document outlining acceptable behavior and/or items that may be brought on site, may not include study specific information in the code of conduct documents. Any reference to a specific study will be considered part of the recruitment process and is subject to IRB review and approval.

You may wish to confer with the Sponsor prior to using any generic materials, as they may request that you obtain IRB approval. Generic items may be submitted via email to info@sterlingirb.com.Revisions to approved generic materials must be reviewed and approved before use. Approval of generic materials is valid for one year. Expired generic materials should not be used.

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

Referral Fees: Sterling IRB does not support the recruitment of research subjects by payment to the Principal Investigator, Sub-Investigator, Clinical Coordinator(s), or other healthcare professionals for patient referrals. This is in accordance with the American Medical Association Code of Medical Ethics which states, “Physicians may not accept payment referring a patient to a research study” and “Physicians should not accept payment solely for referring patients to research studies”; the World Medical Association International Code of Medical Ethics which states, “A physician shall not receive any financial benefits or other incentives solely for referring patients”; and the American College of Physicians Ethics Manual which states, “Giving or accepting finder’s fees for referring patients to a research study generates an unethical conflict of interest for physicians”. In addition, state law may prohibit such practices. Payment or reimbursement should be directly related to performance of the research and at a rate not exceeding the fair-market value for the level of activity performed. The IRB may approve proposals to reimburse a physician a reasonable amount for their time spent reviewing medical records to determine study eligibility. Payment to subjects for referring others may be considered by the Board on a case-by-case basis.

Incentives and Bonus Payments for Recruitment: Fees paid based on the timing or rate of participant enrollment are prohibited unless they are judged not to interfere with providing prospective participants with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on the Principal Investigator or participants. 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. AMA Code of Medical Ethics 7.1.4 Conflicts of Interest in Research

Chapter 6 – CONTINUING REVIEW

Continuing review will occur at intervals appropriate to the degree of risk as determined by the IRB. For FDA regulated research and research subject to the pre-2018 Common Rule, continuing review must occur at least annually. For research that is not FDA regulated and subject to the revised 2018 Common Rule, continuing review is not required (unless the IRB determines otherwise) when a study is eligible for expedited review or has progressed to the point that it involves only one or both of the following:

(A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Sterling IRB handles the continuing review of the study, as well as participating investigative sites, as one entity. Regardless of when the Principal Investigator/Site was approved, all Principal Investigators/Sites will have the same expiration date as established during initial or continuing review. Continuing review will consist of Study Status Reports from the Principal Investigators/Sites and/or the Sponsor/CRO concerning the conduct of the study. The Study Status Report requires 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[3]: 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.).

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

A. Study Status Report: *(Application for Continuation)*

Sterling IRB will typically send reminder notices *(via e-mail or SilverLink)* regarding the study's expiration date and continuing review due date. However, it is the Sponsor and/or Principal Investigator's responsibility to submit the Study Status Report in sufficient time to permit review and approval prior to the study expiration date. The Study Status Report becomes available for submission 60 days prior to expiration. **It is required that the Study Status Report be submitted no less than 30 days prior to the study**

[3] 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.

expiration date as the regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval.

Sterling IRB will send continuing review approval documentation to the Sponsor and study site(s) which includes the study expiration date as well as the due date for the next continuing review report.

B. Final Report:

When a research study no longer involves human subjects, the study may be closed with the IRB. Research involves human subjects while the researchers:

i. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; OR

ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Once the following are true at the site, the site (or Sponsor on the site's behalf) may proceed with submitting the final Study Status Report to formally close from IRB review:

- All subjects at the site have finished their final visits and any follow-up.
- No new data is being collected at the site.
- Analysis of all private identifiable data and specimens is complete at the site.
- The Sponsor or CRO has indicated that the study at the site is closed.

This report should include the date that the final subject completed the study and a summary of the trial's outcome. This report must also be submitted if the study is suspended, cancelled or terminated prematurely and must include the reason(s) for termination or suspension. Furthermore, it is the responsibility of the investigator to also inform the regulatory authority with any reports which are required. Following review, an approval document will be sent to the investigator/site. For multi-site studies, once all participating sites have notified the IRB that the study is complete at their site; the IRB will consider the study to be closed.

Sterling IRB only requires a Final Study Report to be submitted for studies that are approved as human subject research. Sterling IRB does not require final reports from exempt or non-human subject research studies.

C. Lapse in IRB Approval:

Failure to submit a continuing review or final report submission within the federally regulated timeframe constitutes noncompliance with federal regulations governing research involving human subjects. If the Principal Investigator and/or Sponsor does not submit a Study Status Report to Sterling IRB for review prior to the expiration date, the site will be notified via email within 24 hours and by letter within 2 business days that the IRB approval has lapsed. This letter 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**.

Repeated failure to submit a continuing review or final report submission will be considered by the Primary Reviewer and may be brought to the Board for review. The Board may take adverse action against the site/Sponsor including, but not limited to, a finding of serious and/or continuing noncompliance or an unanticipated problem involving risk to subjects or others. Any finding of serious or continuing non-compliance or an unanticipated problem involving risk to subjects or others is subject to mandatory reporting to the applicable regulatory agencies.

D. Reinstatement Requests:

Sterling IRB will consider requests by the Principal Investigator/Site and/or Sponsor/CRO to reinstate the site to active status on an open study following a lapse in approval or premature closure. Reinstatement requests are evaluated on a case-by-case basis. To request reinstatement, please email info@sterlingirb.com.

Chapter 7 – REPORTABLE EVENTS

Many types of events must be reported to the IRB. In general, events that are unanticipated, related to the research, and involve new or increased risk must be reported to the IRB. In addition to the information below, Sterling IRB makes available a summary sheet entitled "Events Reportable to the IRB" on its website at www.sterlingirb.com.

Sponsors and Investigators are responsible for the redaction of all Protected Health Information (PHI) and Personally Identifiable Information (PII) from reportable event documentation prior to submission to Sterling IRB.

A. Protocol Deviations:

Protocol deviations are study events where the Sterling IRB-approved research protocol has not been followed.

DEFINITIONS:

Protocol 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 Protocol 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.

It is the principal investigator's responsibility to assess whether an event constitutes a significant deviation. Sterling requires only the submission of significant deviations that meet the criteria above.

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, via the Reportable Events Form.

Examples of protocol deviations that may be significant (not an exhaustive list):

Enrollment
- Enrolling a subject outside the inclusion/exclusion criteria without sponsor and IRB approval
- Enrolling a subject before their screening lab(s) is/are received

Informed Consent
- Enrolling a subject without obtaining informed consent or performing tests on a subject prior to consenting that subject
- Failure to execute Informed Consent Form as required by the IRB (e.g., failure to affix all necessary signatures as required by the IRB-approved consent form),
- Consenting a subject with the incorrect version of the ICF

Study Procedures
- Deviations in the administration of study procedures:
  - dosing/intervention errors
  - study drug given to incorrect subject
  - failure to perform study related procedures
  - storing drugs incorrectly/at incorrect temperature

Study drug/device

- Subject on exclusionary, disallowed or concomitant medications without sponsor approval

Safety Monitoring

- Omission or delay of safety monitoring procedures, reports, or letters including untimely reporting of events to the IRB (i.e., not reporting Serious Adverse Events and Significant Protocol Deviations within 10 business days of when the site became aware of the event, not reporting planned protocol exceptions for IRB approval prior to implementation)
- Pregnancy in studies for which pregnancy is strictly to be avoided

All Protocol Deviations will be reviewed and acknowledged.

Non-Significant Protocol 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 Protocol Deviations (not an exhaustive list):

- 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 (unless by a significant amount and/or affects safety)

Sponsor monitors often request that the site send the entire Protocol Deviation/Violation Log. In general, these records or logs do not require submission to Sterling IRB.

B. Sponsor-Granted Exceptions:

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.

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). Exceptions necessary to eliminate apparent immediate hazard to human subjects should be reported within 10 business days after initiation.

When the research involves an investigational device, any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency should be reported to the IRB no later than 5 working days after the emergency occurred. Except in such an emergency, FDA pre-approval is also required [21 CFR 812.150 (4)] for any changes or deviations that may affect the scientific soundness of the investigational plan or the rights, safety, or welfare of the subjects.

All Sponsor-Granted Exceptions should be reported using the Sponsor-Granted Exception Report. **Exceptions must be submitted to the IRB accompanied by documentation of the Sponsor's approval thereof.**

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.

C. Serious Adverse Events (SAEs):

The Principal Investigator is responsible for reporting Serious Adverse Events (SAEs) to Sponsors and Sterling IRB; however, they may delegate the data collection and communication of such events to appropriate clinical site research personnel.

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; results in 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.

SUSAR: An adverse reaction that meets three criteria: *Suspected, Unexpected,* and *Serious.*

Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction.

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

Sterling IRB requires that all Serious Adverse Events (SAEs) that are *unexpected* and *related or possibly related to participation in the research* be submitted within 10 business days of when the site becomes aware of the study event via the Reportable Events Form. SAEs meeting the aforementioned criteria that are fatal or life-threatening should be reported immediately to Sterling IRB. The Principal Investigator is responsible for the immediate reporting of all SAEs, including fatal or life-threatening events 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 all suspected unexpected serious adverse (SUSAR) 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).

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.

D. External Adverse Events (IND Safety Reports[4])*:*

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.

Only those IND Safety Reports that may, in the opinion of the Sponsor/CRO/SMO or Principal Investigator, represent an unanticipated problem involving risks to subjects or others should be reported to Sterling IRB. *Generally, an adverse event observed during the conduct of a study would be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.*

For multi-site studies, Sterling acknowledges that the Sponsor is in a better position to process and analyze the significance of adverse event information from multiple sites and to make a determination about whether an adverse event is an unanticipated problem. Accordingly, 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 may represent an unanticipated problem involving risks to subjects or others.

All external adverse events reports that may represent an unanticipated problem involving risks to subjects or others should be submitted to Sterling IRB within 10 business days of receipt via the Reportable Events Form. When safety reports that do not constitute an unanticipated problem are submitted, Sterling IRB will provide an acknowledgement of receipt to the sponsor and all open sites.

E. Unanticipated Adverse Device Effects (UADE):

Investigators are required to submit a report of a UADE to the Sponsor and IRB as soon as possible, but no later than 10 business days after the investigator first learns of the event. The Sponsor must immediately conduct an evaluation of the UADE and report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

DEFINITION:

Unanticipated Adverse Device Effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

F. Unanticipated Problems (Other):

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. If the Board determines that the event represents an unanticipated problem involving risk to subjects or others, the Principal Investigator, Sponsor, and applicable regulatory agencies will be notified within 10 business days.

[4] 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 and CIOMS Reports.

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

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

2. Related or possibly related: to participation in the research (*possibly related* means 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.

An event, incident or problem that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

Examples of other unanticipated problems that do not fall within the classifications for Serious Adverse Events, External Serious Adverse Events, or Significant Protocol Deviations may include, but are not limited to the following:

- New or Increased Risk
- Unexpected frequency or severity of expected adverse events
- Any event that requires prompt reporting according to the Sponsor
- Any accidental or unintentional change to the IRB approved protocol that involved risks or has the potential to recur
- Any change to the research protocol or plan taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
- Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff.
- Breach of confidentiality or privacy
- Untimely destruction of study records
- State Medical Board Action (including suspension, restriction, probation, or revocation of medical license and medical board orders or consent agreements)
- Audit, inspection, or inquiry by a federal agency
- Written reports of federal agencies (e.g. FDA Form 483, Warning Letters, NIDPOEs)
- Termination or suspension of the study without prior agreement of the Sponsor (Sterling IRB and the Sponsor must be notified)
- Incarceration of a study subject not approved to involve prisoners
- Willful or knowing misconduct on the part of the investigator(s) or study staff
- Changes in study status (including any change in the regulatory approval status of the test article, FDA clinical holds, and any study hold/suspension or termination imposed by the Sponsor/CRO, investigator, other reviewing IRB or government agency)[5]
- other government agency, or other party
- Any information in study results, site monitoring reports, and IDMC/data safety monitoring committee/board reports that could directly affect the safety or medical care of past or current study subjects or influence the conduct of the study (These findings should be reported up to two years after the completion of the study)

[5] The notification/report to Sterling IRB must include a summary of the reason(s) for the hold/suspension/termination and provide adequate information for the IRB to assess the impact to study subjects. When an FDA Clinical Hold, or any other study hold/suspension is lifted, Sterling IRB must be notified. The notification/report to the IRB should include a summary of how the issue(s) was resolved and any modifications that were made to the study documents as a result (e.g. a protocol amendment).

- New information that may affect adversely the safety of the participants or the conduct of the clinical trial
- Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

The Principal Investigator is responsible for reporting Unanticipated Problems to trial Sponsors and Sterling IRB; however, they may delegate the data collection and communication of such events to appropriate clinical site research personnel. **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 via the Reportable Events Form.**

It is the IRB's responsibility to determine whether or not an event is an unanticipated problem involving risk to subjects or others. If the Board determines that the event represents an unanticipated problem involving risk to subjects or others, the Principal Investigator, Sponsor, and applicable regulatory agencies will be notified within 10 business days.

G. Noncompliance:

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 Handbook, and in any determination of the IRB) as well as all regulatory requirements on the federal, state and local level.

DEFINITIONS:

Noncompliance: Failure to comply with applicable federal/state regulations or institutional policies governing human subjects research; failure to comply with the requirements or determinations of the IRB.

Serious Noncompliance: Noncompliance that, in the judgment of the IRB Chairperson or designee, or the IRB, increases the risks to subjects, adversely affects the rights, welfare and safety of the research subjects, adversely affects the scientific integrity of the study, or compromises the integrity of the human research protection program.

Continuing Noncompliance: A pattern of noncompliance by an investigator or study personnel that indicates a lack of ability or willingness to comply with applicable federal/state regulations, institutional policies governing human subjects research, or the requirements/determinations of the IRB, that in the judgment of the IRB Chairperson or designee, or the IRB, shows that noncompliance has been ongoing and/or suggests the likelihood that noncompliance will continue without intervention.

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.

Sterling IRB has policies and procedures in place to determine whether each report of noncompliance has a basis in fact, and whether each report constitutes serious or continuing noncompliance. When reviewing reports of noncompliance and unanticipated problems involving risk to subjects or others, Sterling IRB may consider suspension or termination of the research, notification of current participants when such information might relate to participants' willingness to continue to take part in the study, or other appropriate actions to protect the rights, safety and welfare of subjects and/or others.

If IRB approval is suspended or terminated, Sterling IRB will:

- Consider actions to protect the rights and welfare of currently enrolled subjects
- Consider whether procedures for withdrawal of enrolled subjects take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another Principal Investigator, and continuation in the research under independent monitoring)
- Consider informing current subjects of the termination or suspension

- Have any adverse events or outcomes reported to the IRB

The Sterling IRB Chairperson, Vice-Chairperson, and Medical Director are authorized to suspend or terminate research on an urgent basis for the imminent protection of human subjects. Any such actions will be reported and reviewed by Sterling IRB.

Chapter 8 – INFORMED CONSENT

A. The Process of Consent and Assent*:*

Informed consent for a research study is an ongoing 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 should be clear and concise and 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 authorized representative, use of exculpatory language (anything through which the subject or the subject's legally authorized 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. The consent process should occur in an atmosphere that minimizes possible coercion or undue influence. 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 fundamental purpose of IRB review and approval of the consent document is to protect the rights and welfare of human subjects. 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. Varied approaches (e.g. text, images, videos, and other interactive methods) may be used in the informed consent process. The consent document should be revised if protocol changes warrant it or new safety information becomes available that affects the risks to the participants.

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. The absence of expression of agreement or disagreement should not be interpreted as assent. Sterling IRB usually requires that individuals who are unable to provide legally effective informed consent on their own, assent to participation whenever possible, and sign and date a written informed consent / assent document. For research involving minors, Sterling IRB requires that a separate documented assent be obtained from children ages 7–11. Children 12 and older may document assent on the informed consent / parental permission form. However, the Sponsor may increase the required age range for a separate assent to older than 11. Documented assent for subjects younger than 7 years of age is generally not permitted. The assent should be written at an age-appropriate level. Unless informed consent has been waived, if a child reaches the legal age of consent while enrolled in a study, legally effective informed consent should be obtained from the now-adult subject.

Obtaining consent remotely may be considered where appropriate.

B. Elements of Informed Consent*:*

Sterling IRB requires that the informed consent form contain all elements of consent required by regulatory agencies. The basic elements of informed consent are found in 45 CFR 46.116 and/or 21 CFR 50.25. The International Conference on Harmonisation's Guidelines for Good Clinical Practice (E6) include additional requirements for informed consent. Accordingly, Sterling IRB observes the following requirements for consent forms:

The informed consent for FDA-regulated clinical investigations of drugs, devices, and biologics (collectively *medical products*) and HHS-supported or conducted nonexempt human subjects research should begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.

- The fact that consent is being sought for research and that participation is voluntary.
- The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research.
- The reasonably foreseeable risks or discomforts to the prospective subject.
- The benefits to the prospective subject or to others that may reasonably be expected from the research; and

- Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.

  Please note, the key information does not need to be repeated later in the ICF if the information satisfies the basic elements or additional elements of informed consent (under 45 CFR 46.116[b] and [c]),

Sterling IRB considers consent forms with 5 or fewer pages to be concise and focused enough that they don't require a distinct key information section.

Required Elements:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- Description of the study procedures to be followed (including all invasive procedures).
- The trial's investigational product(s) and the probability for random assignment to the investigational product
- Identification of any procedures which are experimental.
- A statement of approximate number of subjects involved in the study.
- The expected duration of participation.
- What is expected of the participants
- A description of any foreseeable risks, discomforts or inconveniences for the subject (includes risk of ineffective treatment, if any).
- A description of any benefits to the subject or to others that may reasonably be expected from the research. When there is no intended clinical benefit to the subject, this should be disclosed.
- A disclosure of appropriate alternative procedures or courses of treatment (if any) that may be advantageous/available to the subject, including their important potential benefits and risks.
- Statement that the monitor(s), auditor(s), IRB and regulatory authority(ies) (specifically the Food and Drug Administration and/or Department of Health and Human Services, if applicable) will be granted direct access to the subject's source records, including medical records, for verification of clinical trial procedures and/or data, without violating the subject's confidentiality to the extent permitted by applicable laws and/or regulations, and that, by signing the consent form, the subject (or legally authorized representative) is authorizing such access.
- Statement that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.
- Statement that, if the results of the study are published, the subject's identity will remain confidential.
- Statement that the trial may be registered on publicly accessible databases, per applicable regulatory requirements.
- An explanation as to whether any compensation is available if injury occurs and, if so, of what do they consist.
- An explanation as to whether medical treatments are available if injury occurs and how to obtain them. This would include reference to who will provide and who will pay for such medical treatment.
- An explanation of whom to contact for answers to pertinent questions (include name, address and phone number):
  - Questions, concerns or complaints about the study to be made to the research staff
  - Questions, concerns or complaints about the study to be made to someone unaffiliated with the study (Sterling IRB contact information)
  - Study-related injury (the Principal Investigator)
  - Subject's rights (Sterling IRB contact information)
- A statement that participation is voluntary.
- A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
- A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- A statement of anticipated circumstances under which the subject's participation may be terminated, including termination by the investigator without regard to the subject's consent.

- Information concerning financial compensation to subjects, including the amount and schedule of payments as well as prorated payments.
- Any additional costs/expenses to the subject that may result from participation in the research.
- The consent may not contain any exculpatory language that waives (or appears to waive) any rights, nor may subjects be asked to release the investigator, sponsor or Institution (or its agents) from liability for negligence.

Additional Elements, required only as appropriate:

- If applicable, reasonably foreseeable risks to the participant's partner, an embryo, fetus or nursing infant
- A statement that the particular treatment or procedure may involve risks to the subject which are currently unforeseeable.
- A statement that the particular treatment or procedure may involve risks that are currently unforeseeable to an embryo or fetus, if the subject is or may become pregnant.
- A statement that significant new findings that develop during the research and that may relate to the subject's willingness to continue participation in the study will be provided to the subject or their LAR.
- The consequences of a subject's decision to withdraw from the research (e.g., termination of life sustaining investigational medical equipment or withdrawal of study agent).
- The procedures for orderly termination of participation by the subject (e.g., at closure of active treatment, study closure or if they withdraw from participation).
- A description of the follow-up procedure for participants who stopped taking the investigational product, withdrew from the trial or were discontinued from the trial.
- A description of the process by which the participant's data will be handled, including in the event of the withdrawal or discontinuation of participation.
- A statement that trial results and information on the participant's assigned treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor.
- For non-FDA regulated research, a statement that biospecimens (even if identifiers are removed) may be used for commercial profit; inform subject whether they will share in this commercial profit.
- For non-FDA regulated research, a statement about whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions. (This provision is intended to pertain to all clinically relevant research results, including general or aggregate research findings and individual research results.)
- For non-FDA regulated research, a statement of whether the study may include whole genome sequencing (the sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
- The following statement must be included in the informed consent document for applicable clinical trials, "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time." FDA has provided guidance on what is considered an "applicable clinical trial."
- Patient Bill of Rights Statement (required in California, see APP028). *Sterling does not require review and approval of the California Experimental Subject's Bill of Rights.* Sterling IRB forms are available on our website.
- HIPAA compliant (see IRB039).
- Signature / date of the witness to the oral presentation of informed consent (if required).

Additional Elements, required for studies subject to the Revised Common Rule:

- For research that involves the collection of identifiable private information or identifiable biospecimens, the ICF must contain *one* of the following statements:
    - A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative

      OR

- A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Sterling IRB Additional Requirements:

- If LAR is used, statement that "you/your references in consent form refer to participant rather than legally authorized representative"
- Where applicable, amount of blood drawn.
- Where applicable, disclosure if animal studies have not been conducted.
- Where applicable, warnings regarding keeping study articles out of reach of children.
- Where applicable, explanation of blinded study design and information available in emergency situations.
- Information as to whether the study article or intervention will be available after the study has ended
- Where inclusion of language concerning the pregnancy of a partner is applicable, a statement that the particular treatment or procedure may involve risks that are currently unforeseeable to an embryo or fetus.
- A statement that the participant should discuss acceptable contraception options with the study doctor. Please note, if the protocol addresses specific forms of contraception, the specific forms of contraception must be included in the ICF or presented to the participant by another means.
- A statement regarding pregnancy testing if required by the protocol. Please note, Sterling IRB requires all pregnancy testing required by the research to be added to the protocol and ICF.
- A statement regarding sperm donation. This is not required to be stated in the protocol.
- The study sponsor (or sponsor representatives) and other doctors, health care professionals or research staff who are involved in the study will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the subject's confidentiality to the extent permitted by applicable laws and/or regulations, and that, by signing the consent form, the subject (or legally authorized representative) is authorizing such access.
- Dated signature lines to permit verification that consent was obtained from subject (or LAR, as applicable) prior to participation in any study related procedures.
- Document written in a language understandable to the subjects (for most studies, this would be approximately an 8th grade readability level). Sterling IRB will determine, based on the information in the protocol and on the application if the readability scale must be adjusted lower. Sterling IRB will make every effort to keep the reading level at or below an 8th grade reading level.
- Where appropriate, the term "participant" or "subject" is used instead of "patient."
- The term "treatment" is defined
- Required language (header or footer) concerning IRB approval dates and version numbers
- Header and Footer language per site standards (if applicable).
- Information regarding the following, as applicable:
  - Future Research
  - Disclosure of Results
  - Photographs, audio or video recording
- A statement that the participant will be provided a copy of the signed and dated consent form (external regulations/guidelines dictate that the subject/LAR receive a signed/dated copy, IRB requirements further require that this be detailed in the consent form).
- Lines for the signature/ date of all applicable persons. See Section L. Signature Requirements.

Please note, for studies subject to the Revised Common Rule, personal private information may be obtained without consent if it is obtained through oral or written communication with the subject and identifiable information and identifiable biospecimens may be obtained without consent by accessing records or stored specimens.

Sterling IRB may employ additional consent requirements beyond those contained in regulations/guidelines (e.g., preferred language, a method to verify participants have received/reviewed consents in their entirety, etc.)

Non-Disclosure Agreement (NDA)/Confidentiality Agreement (CDA) in Research:

Study participants may not be asked to sign a non-disclosure agreement (NDA)/confidentiality agreement (CDA).

No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. --- (45 CFR 46.116 and 21 CFR 50.20)

The non-disclosure agreement is designed to protect a business's confidential information. A study consent form is designed to provide a potential research participant with adequate and accurate information that allows them to make an informed decision about whether or not to participate in a research study.

NDAs and CDAs have no place in the research consent process and cannot be used in studies under Sterling IRB review. Sterling IRB will not review or approve such documents to be given to study participants. Any NDA/CDA language included in submitted consent documents will be removed in the IRB consent editing process.

C. Authorization to Use and Disclose Medical Information

Sterling IRB will review HIPAA authorization language when the information is included in or appended to the consent form.

A stand-alone HIPAA authorization (for research) is a document that is used to obtain permission from an individual for a covered entity to use and/or disclose the individual's identifiable health information for a research study, and that is not combined with an informed consent document to participate in the research study itself. Stand-alone HIPAA authorization forms do not require IRB review and approval. However, Sterling IRB will review stand-alone HIPAA authorization forms upon request.

It is the responsibility of the investigator and site to comply with all HIPAA requirements.

A valid authorization must contain at least the following elements (core elements):

- A description of the information to be used or disclosed.
- Person(s), or class of persons, authorized to make the requested use or disclosure.
- Person(s), or class of persons, to whom the covered entity may make the requested use or disclosure.
- Purpose of the requested use or disclosure.
- An expiration date or an expiration event that relates to the individual of the purpose of the use or disclosure. The statement "end of the research study," "none," or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the creation and maintenance of a research database or research repository.
- Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided.

In addition to the core elements, the authorization must contain statements adequate to place the individual on notice of all of the following:

- The individual's right to revoke the authorization in writing
- The consequences to the individual of a refusal to sign the authorization
- The potential for information disclosed pursuant to the authorization to be subject to redisclosure by the recipient and no longer be protected

D. Waiver or Alteration of Informed Consent*:*

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

1. Waiver of Elements of Consent: The IRB may consider waiving the requirement for some or all of the elements of informed consent. The regulations (45 CFR 46.116 and 21 CFR 50.22) state that informed consent may be waived in full or in part if the IRB determines that:

   a. The research, or clinical investigation, involves no more than minimal risk to the subjects;
   b. The research, or clinical investigation, could not practically be carried out without the waiver or alteration;
   c. If the research, or clinical investigation, involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
   d. The waiver or alteration will not adversely affect the rights and welfare of the subjects; **and**
   e. Whenever appropriate, the subjects or legally authorized representative will be provided with additional pertinent information after participation.

   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.

   To request a waiver or alteration of informed consent, please complete the *Request for Waiver or Alteration of Informed Consent*.

2. Waiver of Documentation of Informed Consent: the regulations (45 CFR 46.117(c)(1)(ii) and 21 CFR 56.109(c)(1)) state that the IRB may waive the requirement for the investigator to obtain a signed consent form if it finds that:
   - The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Waiver of Documentation of Informed Consent: the regulations (45 CFR 46.117(c)(1)(i)(iii)) (*not applicable under FDA regulations*) state that the IRB may waive the requirement for the investigator to obtain a signed consent form if it finds any of the following:
   - 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 (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. **or**
   - The subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

To request a waiver of documentation of informed consent, please complete the *Request for Waiver of Documentation of Informed Consent*. **A waiver of documentation of informed consent is not permissible for research regulated by Health Canada or being conducted in the Province of Quebec.**

Even if the waiver of documentation is granted, Sterling IRB may require the Principal Investigator to provide subjects with a written statement regarding the research. The oral or written information provided to participants must include all required and appropriate additional elements of consent disclosure.

E. Re-consenting*:*

During the conduct of a study, it may be necessary to revise the consent form to include new information or changes to the protocol. All revisions to the informed consent must be reviewed and approved by Sterling IRB. Any changes that could affect a subject's willingness to continue their participation in the study will require the re-consent of all currently enrolled subjects. The FDA and Sterling IRB do not require the re-consent of subjects that have completed their active participation in the study unless the changes relate to risks to previously enrolled subjects. When new and/or revised consent documentation is approved by the IRB, subjects should be re-consented at their next scheduled study visit (as detailed in the schedule of events in the IRB-approved protocol) unless the IRB approval document includes specific directives. If the consent form is revised multiple times within a short timeframe, Sterling IRB allows for the most current consent form to be signed by all current and new enrollees provided that current enrollees are informed of all revisions made between each consent version.

To prevent delays in the reconsent of subjects, sites should consider the following actions:

- Review subject visit schedules to ensure that subjects are reconsented at their next scheduled study visit
- Make copies of the revised consent form upon receipt by the IRB
- Remove the old consent form from use when the revised consent form is received from the IRB
- Perform/receive any necessary training or familiarize staff with the protocol and consent changes that do not require additional training
- Ensure that all relevant site staff are aware that a revised consent form is forthcoming

Any changes to study procedures that require the reconsent of subjects should not be implemented until the subject has agreed to continue in the study.

If there have been no changes to the informed consent, the regulations and the IRB do not stipulate that a subject must be reconsented after a certain time has elapsed from the consent of the subject to the initiation of study procedures. However, if there is a concern that the subject does not remember the information that was previously provided about the study, the informed consent process should be repeated, and the informed consent form should be reviewed with the subject.

F. End of Participation or Subject Withdrawal from a Study

When a participant decides to stop treatment with the investigational product or withdraw from a trial; is discontinued from the trial; or reaches the routine end of the trial, the investigator should follow the protocol and related documents. For participants who did not reach the routine end of the trial, this may include instructions to avoid loss of already collected data, to ensure that trial results are reliable.

After providing consent, a subject may decide to prematurely terminate his or her participation in a research study. Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a research study, the investigator should make a reasonable effort to ascertain the reason while fully respecting the subject's rights. To minimize withdrawal, investigators may consider discussing participant concerns and explaining the value of continuing their participation. However, this should only be done in a manner that does not unduly influence the participant's decision.

With respect to the participant's preference to be informed, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding.

For FDA-regulated trials, the Investigator is advised to observe the following with regard to data retention when participants withdraw from a clinical trial:

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

Please also refer to FDA's *Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials* for additional information.

G. Subject Compensation*:*

Payments to participants should be timely, prorated, to avoid any impression of coercion to continue in the study, and not wholly contingent on completion of the trial. In general, if a completion bonus is offered to study participants, this amount should not exceed 25% of the total compensation amount. 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. Reasonable reimbursement of expenses incurred by participants, such as for travel and lodging, is not coercive.

All information concerning compensation and reimbursement should be detailed in the informed consent document. Alternative payment methods (methods other than cash/check) should be detailed in the consent form, as method of payment could impact a participant's willingness to participate. Compensation and reimbursement should be equal for all subjects at each site. Sterling IRB is available to assist with preparing informed consent language or an informed consent addendum regarding subject compensation or reimbursement. Please contact Sterling IRB if you have any questions.

The Board gives special consideration to vulnerable populations where others are acting as their legally authorized representatives, that decisions to participate are not based on monetary gain. For studies involving children/minors, compensation is reviewed by Sterling IRB on a case-by-case basis as the suitability of a particular payment plan is protocol-specific. Compensation may be offered to the parent/guardian and/or the child for the time and inconvenience of participating in the research. Any payments offered must be of an amount that is not so excessive that it compromises the examination and evaluation of risks by the parent/guardian or child or causes the parent/guardian to exert pressure on the child to participate. When planning payments to children, age and maturity should be considered. For younger children, a non-monetary gift of appreciation such as a toy may be more appropriate.

H. Non-English Speaking Subjects and Translations*:*

The informed consent document and all subject materials must be presented in a language understandable to the subject or legally authorized representative. If the subject does not speak English, Sterling IRB requires a certified translation of the IRB approved informed consent. 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.

Some Sponsors require back translations for accuracy. Any revisions to the informed consent that require translation must go through the certified translation process. Sterling IRB may make minor changes that do not require translation (such as number of participants, name, phone numbers, etc.) without going through the certification process.

When the informed consent(s) or any subject-facing materials are revised and there are active non-English speaking subjects, it is Sterling IRB's expectation that these documents are submitted for translation within 30 days of IRB approval of the English version(s) of the document(s).

The person obtaining the informed consent must be fluent in both English and the language of the subject. If the research staff does not speak the language of the prospective subject, a professionally trained interpreter should assist in the translation process. A family member of the prospective subject is not acceptable. This is to ensure completeness of the consent process and that all questions and answers are translated fully, and no information is abbreviated or omitted. When subsequent visits are minor in nature (not involving difficult procedures) a family member, or friend may serve as the interpreter.

Sterling IRB allows the use of a short form in applicable situations for subjects who do not speak English. See the section on Short Form Consent below.

Sterling IRB may also translate documents for sites not under Sterling IRB review. These are known as "pass-through" submissions. Pass-through submissions are eligible for translation services only and are not eligible for Sterling IRB review. To inquire about pass-through service requirements and costs, please email info@sterlingirb.com.

I. Short Form Consent*:*

If a non-English speaking prospective participant requests to enroll in a study and there is insufficient time to obtain a translated study consent, the regulations allow researchers to provide non-English speaking potential participants with an oral presentation of the informed consent information in conjunction with a written short form consent document and a written summary of the oral presentation (a copy of the English version of the study consent form may serve as this summary). A Short Form is a consent document written in a language understandable to the non-English speaking prospective participant that summarizes the required elements of informed consent but does not contain specific study information. A short form consent is intended only to be used when time is of the essence, and a translated consent form is unavailable. If your site reasonably expects that the subject population for your study will include individuals who do not understand English and can anticipate the specific language(s) that they will understand, the consent form should be translated appropriately into that language.

Short form templates, translated into multiple languages, are available via SilverLink (login required) on the left panel under "Useful Links". Sterling IRB has already approved these forms, so no additional Sterling IRB approval is needed to use these forms. For multisite studies, it is recommended that sites consult with their Sponsor/CRO regarding the use of short forms. If your site should require a language not available, please contact Sterling IRB.

The following guidelines should be used when utilizing a short form:

1. When this procedure is used for subjects who do not speak English,

a. The oral presentation and the short form written document must be in a language understandable to the subject, and
b. The witness should be fluent in both English and the language of the subject.

2. At the time of consent,
   a. The short form document should be signed and dated by the subject or subject's LAR.
   b. The written summary should be signed by the person obtaining informed consent.
   c. There will be a witness to the oral presentation. The witness should be an impartial third party, one who is not connected with the research (for example, a non-research team employee, or a relative of the participant, or person similarly unconnected with the research).
   d. The witness should sign the short form document and a copy of the written summary.
      i. The witness should sign the short consent form to attest to the accuracy of the presentation and the apparent understanding of the subject.
   e. The witness must be fluent in the subject's language as well as English. When an interpreter assists the person obtaining consent, the interpreter may serve as the witness.
   f. A copy of the written summary shall be given to the subject or the LAR, in addition to the short form.

Use of a short form consent does not meet the requirements for a valid authorization under the HIPAA Privacy Rule. Authorization should be obtained from the subject using a translated authorization form.

When informed consent has been obtained via the short form method, the investigator must promptly (within 30 days) obtain a translated copy of the IRB-approved consent form. Once the translated consent form is reviewed and approved by the IRB, the subject should be reconsented with the translated consent form as soon as possible (within 60 days of receipt or at the next scheduled visit, whichever occurs first).

For research subject to the revised Common Rule, the short form written consent document must state that the key information included in the "concise explanation" was presented to the subject or their LAR prior to other information being provided.

The IRB requires reporting on the use of a translated short form consent on the site's next Continuing Review via the Study Status Report.

J. Subject Contact with Sterling IRB*:*

It is the responsibility of the Principal Investigator to explain the role of the IRB to prospective subjects. The IRB's contact information is 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.

K. 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. *Screening Tests Prior to Enrollment FDA Information Sheet. Guidance for Institutional Review Boards and Clinical Investigators.*

L. Signature Requirements*:*

<u>The informed consent process may involve a physical or an electronic signature and date.</u>

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 the consent document.

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 when dictated by the circumstances of the consent process (refer to instructions for use of the witness signature line on the IRB-approved consent form and/or refer to state/local requirements)

Impartial Witness Signature: If a research subject or legally authorized representative is unable to read the consent form because of blindness, illiteracy, or some other reason, an impartial witness not affiliated with the research or investigator should be present during the entire consent process and should sign and date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or subject's legally authorized representative, and that consent was freely given by the subject or the subject's legally authorized representative. 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. An Impartial Witness Signature Form is also available for use.

Signature of Legally Authorized Representatives (LARs): Both FDA and DHHS define a Legally Authorized Representative 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 research procedures. Dependent 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 may also refer to a 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.

The IRB must approve the use of an LAR. A justification for use of an LAR must be provided to the IRB. Considerations include but are not limited to:

- Protocol eligibility criteria (consent via LAR must generally be explicitly permitted in the protocol)
- Complexity of protocol requirements
- Potential for benefit to the participant
- Whether the research is studying a participant population often requiring a LAR (e.g., Alzheimer's)

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. 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.

For studies subject to the revised Common Rule, if there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

For research involving non-viable neonates, the consent of a LAR for either or both of the parents is not permitted.

Caregivers are not considered human subjects unless data is collected about them. If caregivers are also subjects (e.g., they are answering questions about how they feel as a caregiver), informed consent is required. When caregivers are not subjects (e.g., their role is limited to assisting subjects), informed consent is not required. Documents related to the caregiver's responsibilities do not require submission to the IRB.

M. Remote and Electronic Consent (e-consent)*:*

Remote consent is a method of obtaining informed consent using a paper or electronic consent where the study team and participant are not in the same physical location during the consent process.

Remote consent using a paper consent form is a specific type of remote consent where a copy of the written informed consent form is provided to the participant via email, fax, mail or during a prior in-person visit. The informed consent process may be conducted over the phone or via video conference. The investigator must receive the signed consent form prior to beginning study-related procedures. The participant should sign and date a hard copy of the consent form and may return it to the study team via fax, a photographic image sent through electronic means, scanning the consent form and returning it through a secure email account, or posting it to a secure internet address. The original signed and dated informed consent should then be mailed or brought to the next visit to the site. The person who conducted the consent discussion must sign the informed consent document and note that the discussion occurred via telephone or video conference. The subject or LAR must be given a signed and dated copy of the informed consent form. This method of remote consent does not require IRB approval. However, prior to implementation, sites should confirm with the Sponsor that the use of remote consent is allowed.

Where it is not feasible for investigators to receive the signed consent form prior to beginning study-related procedures, or if your site's proposed consent process does not align with the above, Sterling IRB must review and approve the planned informed consent process.

If obtaining verbal or telephone consent without a written signature, the IRB must have granted a waiver of documentation of consent.

Electronic consent (e-consent) can refer to the process by which a participant's signature is obtained and documented electronically, and it can also refer to other aspects of the informed consent process. E-consent can describe the exact representation of the IRB-approved document on an electronic device as well as refer to a consent process using electronic devices and audio-visual aids.

E-consent may be a method of obtaining informed consent using an electronic signature or system instead of a paper consent form. When an e-consent system is used, the consent process can occur in-person or remotely. E-consent may be used to provide information usually contained within the written informed consent document, evaluate the subject's comprehension of the information presented, and document the consent of the subject or the subject's LAR. Sterling IRB must review and approve the e-consent to ensure applicable regulatory requirements have been met.

Electronic informed consent may also refer to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent. The suitability of this method of obtaining consent should be considered based on the population being enrolled.

An electronic signature is a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

The investigator is responsible for ensuring that legally effective informed consent is obtained before that subject takes part in the study. Whether part or all of the e-consent process takes place on-site or remotely,

the responsibility for obtaining informed consent remains with the investigator and the study personnel to which responsibility has been appropriately delegated. The investigator cannot delegate authority to obtain informed consent to the electronic system.

The regulatory requirements under 21 CFR parts 50 and 56 and 45 CFR part 46 remain the same regardless of whether an electronic process, electronic informed consent, or electronic signature is utilized. Investigators must ensure that they follow institutional policy and applicable federal, state, and local laws governing the use of electronic signatures.

The following information details Sterling IRB's submission requirements and process for evaluating the use of electronic informed consent:

1. The person obtaining consent should assure themselves of the identity of the subject (or the subject's LAR) or the electronic system must include a method to ensure that the person electronically signing the informed consent is the subject who will be participating in the research study or is the subject's LAR.
   Examples of verification methods include:
   a. Using information from some form of official identification, such as a birth certificate, government-issued passport, or driver's license
   b. Use of security questions
   c. Use of PIN provided by the study team
   d. Use of strong digital login credentials accompanied by multi-factor authentication
   e. Use of video observation or other visual methods
   f. Use of biometric methods

   For research that is not FDA-regulated, it may not be possible or necessary for all types of research to verify subject or LAR identity. Sterling IRB will apply a risk-based approach to the consideration of this requirement.

2. The investigator should have methods in place to ensure that the e-consent process allows subjects the opportunity to consider whether or not to participate and ask questions about the study before signing consent as well as at any time during the subject's involvement in the research. This may be accomplished by in-person discussions with study personnel or through a combination of electronic messaging, telephone calls, video conference, or a live chat with a remotely located investigator or study personnel.

3. The subject (or the subject's LAR) must be provided with a copy of the signed and dated informed consent document. The copy provided to the subject can be paper or electronic.

4. Sterling IRB should receive copies of all forms (electronic and paper) and informational materials that will be presented to subjects during the e-consent process. This includes scripts, storyboards, videos, and web-based presentations.

   a. Sterling IRB only requires review of the template version of the paper or electronic materials. Screenshots generally do not require IRB review if the IRB-approved document is exactly represented on an electronic device. (This also applies to other participant-facing documents that require IRB review, such as diaries and questionnaires.) Please note, the IRB may request that screenshots be submitted on a case-by-case basis.

5. Sterling IRB must review and approve the final e-consent and any subsequent amendments to the e-consent. However, Sponsors and sites may wish to obtain IRB approval of the consent document text prior to finalizing development of the e-consent.

6. Any differences between the e-consent and the IRB approved consent document must be described in the e-consent submission.

7. For a multi-site study, e-consent must be reviewed and approved at the sponsor/study level. If the e-consent has been reviewed and approved at the sponsor/study level, and the site is using the sponsor's system, Sterling IRB does not require submission of the e-consent for each site. If a site is using a different e-consent system/process, different informational materials from the sponsor, or has made site-specific changes to the Sponsor's template consent language, submission at the site-level is required.

8. The e-consent should include a method for version control. Sterling IRB recommends using the version information from the IRB approved consent document.

9. When computerized systems are used to obtain informed consent, participants may be given the option to use a paper-based approach as an alternative.

10. If the research is FDA regulated and does not meet the criteria for a waiver of documentation of consent (i.e., the study poses more than minimal risk to the participants), the FDA requires that the e-consent system be Part 11 compliant (21 CFR Part 11).

11. For non-FDA regulated research, informed consent or the documentation of consent may be waived for minimal risk research meeting the requirements at 45 CFR 46.116(d).

For additional information regarding e-consent, FDA and HHS published a joint guidance in December 2016 titled, "Use of Electronic Informed Consent - Questions and Answers".

N. Charging Subjects for Study Participation ("Pay to Participate Studies")

The informed consent form must include a description of any additional costs to the subject that may result from participation in the research. The IRB will review the consent form to ensure that any such charges are appropriate and equitable. Other than the limited circumstances in which the FDA permits a Sponsor to charge a subject for an investigational product, Sterling IRB does not review studies that require a subject to pay to participate. See the FDA's Guidance on *Charging for Investigational Drugs Under an IND* and FDA's FAQs about Investigational Device Exemption *Charging for Investigational Devices* for additional information.

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 authorized 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. 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.

A. Children and Minors*:*

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. If research on a specific treatment involves solely treatments or procedures for which minors can give consent outside the research context (under applicable state and local laws, for example, research on sexually transmitted diseases or pregnancy), such individuals would not meet the definition of children as defined at 45 CFR 46.402(a). Thus, subpart D would not apply to the research and parental permission (or waiver thereof) is not a consideration for these minors. Under these circumstances, minors may provide their own informed consent.

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 guardians. Sterling IRB must determine whether the permission of one or both parents is required, based on the expected level of risk and prospect of direct benefit to the child. Children should always be asked if they want to participate in the research and must affirmatively agree to participate. In certain studies, the IRB may waive assent requirements for some, or all of the children involved in the research. Also see Chapter 8, A. The Process of Consent and Assent.

For research approved under 45 CFR 46.404 (21 CFR 50.51) or 45 CFR 46.405 (21 CFR 50.52), the IRB may find that the permission of one parent is sufficient (if consistent with state law).

For research approved under 45 CFR 46.406 (21 CFR 50.53) or 45 CFR 46.407 (21 CFR 50.54), both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child, if consistent with state law. **Mere inconvenience to reach the second parent to obtain permission is not an acceptable justification for the "not reasonably available" exception.**

For research studies involving multiple arms or cohorts (i.e., placebo-controlled research studies), the IRB must review and determine the pediatric risk for each component of the study. Sterling IRB will determine whether the permission of one or both parents is required based on the strictest pediatric risk category.

B. Pregnant Women, Fetuses, Neonates of Uncertain Viability and Nonviable Neonates*:*

When applicable, Sterling IRB applies federal regulations at 45 CFR 46, Subpart B regarding additional safeguards for research involving pregnant women, fetuses, neonates of uncertain viability and nonviable neonates. Viable neonates are addressed as referenced above in the section on children and minors.

Incidental pregnancies: If a subject becomes pregnant during a study and information regarding the pregnancy will be collected, the IRB will apply the requirements specified at 45 CFR 46 Subpart B. If a subject becomes pregnant during a study and information regarding the newborn will be collected after viability has been determined, the IRB will apply the requirements specified at 45 CFR 46 Subpart D. The requirements will be applied regardless of the source of funding. Such data collection should be described in the study protocol and consent document.

If a subject's partner becomes pregnant during a study and information regarding the pregnancy will be collected, the partner or newborn would not meet the definition of a human subject, nor would the collection of this data be considered a clinical investigation, per the FDA as defined by 21 CFR 50. In most instances, collection of this information does not meet the definition of "Research" under 45 CFR 46. Therefore, if the protocol states that data will be collected on pregnant partners, the main consent form should inform subjects of the plan to collect this data. The IRB will not require the submission of additional documents (e.g., a separate informed consent form (ICF) for pregnant partners, authorization form, information sheet, medical release form). If an additional document is submitted, the IRB will review and approve it as a subject material.

C. Prisoners*:*

A prisoner is an individual involuntarily confined or detained in a penal institution, including persons: (1) sentenced to such an institution under a criminal or civil statute; (2) detained in other facilities (e.g., for the treatment of drug detoxification or alcoholism) by virtue of statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution; and (3) detained pending arraignment, trial or sentencing.

For HHS-conducted or -supported research involving prisoners, the requirements found at 45 CFR 46 Subpart C must be followed.

For studies that were not previously approved to involve prisoners, the IRB should be notified within 10 business days if a subject becomes 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 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.*, intellectual disability) 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. In the situation of the exclusion of cognitively impaired subjects, Sterling IRB will consider the rationale for exclusion if the clinical study may provide direct benefit to this vulnerable group. 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 traumatized and comatose subjects is conducted shall receive IRB consideration because the subjects' ability to provide informed consent is often severely compromised; decisions about participation may need to be made in an expeditious manner and the patient's legally authorized 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 is 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). The above notwithstanding, Sterling IRB does not review emergency setting research of investigational products.

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. Low-Literacy and Physically Challenged Subjects (Visually Impaired/Blind and Hearing Impaired/Deaf):

Visual Impairment: Unable to read because of blindness, illiteracy, or some other reason

Hearing Impairment: A partial or total inability to hear affecting one or both ears

If enrollment of such subjects is allowed, an impartial third party should witness the entire consent process and sign the consent document or Sterling IRB's Impartial Witness Form for Limited and Non-Readers. *See Impartial Witness Signature Requirements in Chapter 8, Section L.*

Subjects who cannot write should indicate their consent by making their mark on the consent form, if consistent with state law. The subject's study records should indicate the reason for a lack of signature.

For subjects who are deaf or hearing impaired, an interpreter or assistive listening device may be needed.

Subjects who cannot read because of blindness, illiteracy, or some other reason but understand English may have the consent read to them. In addition, an audio or video tape recording of the contents of the consent form or a consent form with enlarged font (depending on the level of visual impairment) may be used.

For those in need of an audio recording, PDFs can be "Read Out Loud" from within the PDF. To access the "Read Out Loud" feature of a PDF via Adobe:

- Select 'Menu', 'View', 'Read Out Loud'
- To quickly activate this feature, press Shift + CTRL + Y and click any section of the consent form to start the automated reading
- For more information, visit the Adobe website

It is recommended that the study records include the method in which the consent was reviewed and a description of the specific means by which the prospective subject communicated agreement to take part in the research and how questions were answered.

Sterling IRB does not require a legally authorized representative for participants that are capable of providing consent but physically unable to do so.

H. 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.

I. 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.

J. 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.

K. 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 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: If an employer seeks to enroll employees in a study sponsored or conducted by the employer, the informed consent process should contain safeguards to ensure that participation is voluntary and that the possibility of undue influence or coercion by supervisors, peers, or others is minimized. The employee's decision to participate, or not to participate, should have no effect on their performance evaluations, job advancement, benefits, or employment status. In addition, measures should be taken to protect the confidentiality of the employee's personal medical information or research data. If employees may be enrolled, standard language will be added to the informed consent regarding the inclusion of employees in the research study.

Chapter 10 – 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: https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/HIPAA-ACA/Downloads/CoveredEntitiesChart20160617.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.

A Covered Entity is:

A health plan. An individual or group plan that provides, or pays the cost of, medical care. Health plans include private entities (e.g., health insurers and managed care organizations) and government organizations (e.g., Medicaid, Medicare, and the Veterans Health Administration)

A health care provider. A provider of health care services and any other person or organization that furnishes, bills, or is paid for health care in the normal course of business. Health care providers (e.g., physicians, hospitals, and clinics) are covered entities if they transmit health information in electronic form in connection with a transaction for which a HIPAA standard has been adopted by HHS. (e.g., billing)

A health care clearinghouse. A public or private entity, including a billing service, repricing company, or community health information system, that processes non-standard data or transactions received from another entity into standard transactions or data elements, or vice versa.

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.

A valid authorization must contain at least the following elements (core elements):

- A description of the information to be used or disclosed.
- Person(s), or class of persons, authorized to make the requested use or disclosure.
- Person(s), or class of persons, to whom the covered entity may make the requested use or disclosure.
- Purpose of the requested use or disclosure.

- An expiration date or an expiration event that relates to the individual of the purpose of the use or disclosure. The statement “end of the research study,” “none,” or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the creation and maintenance of a research database or research repository.
- Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided.

In addition to the core elements, the authorization must contain statements adequate to place the individual on notice of all of the following:

- The individual's right to revoke the authorization in writing
- The consequences to the individual of a refusal to sign the authorization
- The potential for information disclosed pursuant to the authorization to be subject to redisclosure by the recipient and no longer be protected

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. Certificates of Confidentiality (CoC*):*

Certificates of Confidentiality (CoCs) protect the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations. NIH funded research that involves the collection or use of identifiable, sensitive information are automatically deemed to be issued a CoC. Researchers may request a CoC from NIH for health-related studies that are not funded by NIH but the issuance of the CoC is at the discretion of NIH.

If a certificate of confidentiality has been issued, information regarding the protections and limitations of the Certificate must be included in the informed consent for the study.

C. 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.

Per FDA regulations, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

HHS regulations do not provide for an emergency use exception to IRB review, though HHS regulations do allow physicians to provide emergency medical treatment to patients. In emergency use situations, HHS regulations do not consider patients to be research subjects, and the outcome of emergency care may not be included in any report of a research activity.

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 Chairperson 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 Chairperson 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 Chairperson (or designee) confirms the presence of the necessary conditions, the IRB Chairperson (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.

If obtaining informed consent prior to use of the test article is not feasible (see 21 CFR 50.23), federal regulations provide an exception from the general requirements of informed consent if the investigator and an independent physician (one who is not participating in the clinical investigation) certify in writing all of the following:

- use of the test article is necessitated by a life-threatening situation
- the subject is unable to provide legally effective informed consent
- there is insufficient time in which to obtain consent from the subject's legal representative
- there is no available alternative method of approved or generally recognized therapy of equal or greater likelihood of saving the subject's life

If, in the investigator's opinion, immediate use of the test article is necessary to save the life of the subject and there is insufficient time to obtain the independent determination required by 21 CFR 50.23(a) before using the test article, the investigator must make their own written determinations, then obtain the written review and evaluation of an independent physician (one who is not participating in the clinical investigation) within five working days after the use of the test article.

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.

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

D. Humanitarian Use Device*:*

A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease that affects or is manifested in not more than 8,000 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. A request for IRB review of a Humanitarian Use Device should be submitted via the Application for Humanitarian Use Device. The application must be submitted prior to review and approval by the Board. The IRB is responsible for initial and continuing review of the Humanitarian Use Device.

E. Expanded Access*:*

Expanded Access is a term used to describe the use of an investigational drug or device outside of a clinical trial for patients suffering from a serious or life-threatening disease or condition when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient’s disease or condition. This type of access has been described in the past as Compassionate Use or Treatment Use. Prospective FDA, Sponsor and IRB approval is required prior to the use. Please contact Sterling IRB to discuss an expanded access request.

F. 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

For studies involving genetic research, Sterling IRB will include information regarding the risks of genetic testing as well as the protections provided by GINA (Genetic Information Nondiscrimination Act), where applicable.

G. Mobile Applications:

A mobile application or “mobile app” is defined as a software application that can be run on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity), or a web-based software application that is tailored to a mobile platform but is executed on a server.

Sterling IRB requires that the protocol or supporting documentation provide detailed information about what the app does and how it will be used in the study. The protocol should include the name of the app and whether it is commercially available or being developed for the current study.

The protocol and informed consent should address what data the app collects including incidental data such as contacts, texts, geo-location information, and photos and how confidentiality will be maintained. The protocol should indicate what data security controls will be implemented to prevent interception of information by a third-party; where the data will be stored; password protections and data encryption.

Subjects should be informed whether they will be required to access the app via a device (e.g., phone, tablet, computer) that will be provided for the study and what happens to the device when the study is complete. If subjects will be required to use their personal device, they should be informed whether they will incur any data usage fees. Subjects should also be informed what support is available should they encounter technical issues.

In general, if research subjects must agree to a terms of use/terms of service, privacy policy or end user license agreement prior to using an app or website for a study, Sterling IRB will not approve such agreements but will request a copy of the agreement to determine if standard language should be included in the consent form. Sterling IRB may include standard language describing the types of information the digital technology may collect and with whom collected information will be shared and indicating that any exculpatory language in the agreement does not release the investigator, sponsor, institution, or agents from their responsibilities, nor does it waive any of the participant’s rights as a research subject.

FDA regulates a subset of mobile apps which meet the definition of “mobile medical app.” A “mobile medical app” is a mobile app that meets the statutory definition of a device and either is intended (1) to be used as an accessory to a regulated medical device, or (2) to transform a mobile platform into a regulated medical device. FDA has stated that the agency intends to exercise enforcement discretion with respect to mobile apps that may meet the definition of a medical device but pose a low risk to participants. For more information, refer to the FDA’s guidance *Policy for Device Software Functions and Mobile Medical Applications.*

H. Subject Transfers*:*

IRB approval is not required for subject transfers. However, both the transferring and receiving site should notify Sterling IRB of subject transfers on the next Study Status Report. Subjects should authorize the release of any protected health information to the new site. In addition, the subject should be presented with the current informed consent and HIPAA authorization for the new site, where applicable. As a reminder, any written information to be provided to subjects for the study should receive IRB review and approval prior to use.

I. Return of Research Results:

The regulations neither require nor prohibit the return of research results to participants. However, plans to return individual research results should be described in the protocol or other study documents, and the consent form. The consent form should include basic information regarding the return of the research results, including a brief description of the information that will be returned, who will provide the information, and when the disclosure is expected to take place.

For studies subject to the revised Common Rule, the consent form must include a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.

Note: IRB review is not required if the decision to return results is made after the study has been closed by the IRB.

J. Research Involving Dietary Supplements:

A dietary supplement is a product taken by mouth that contains a “dietary ingredient” and is intended to supplement the diet. Ingredients may include: (1) vitamins, (2) minerals, (3) herbs or other botanicals, (4) amino acids, (5) substances found in the diet (such as enzymes and edible organ tissues and glandulars), and (6) concentrates, metabolites, constituents, extracts, or combinations of the substances identified in (1)-(5). Dietary supplements may come as tablets, capsules, softgels, gelcaps, liquids, or powders. They are regulated as foods, rather than drugs, and they must be labeled as a dietary supplement. [FD&A Act, section 201(ff)]

Dietary supplements are exempt from FDA regulation as drugs if they are evaluated and/or are labeled solely for structure/function claims. However, if a dietary supplement is evaluated for the diagnosis, prevention, mitigation, treatment or cure of a specific disease or condition (i.e., a disease claim), then an Investigational New Drug (IND) application is required.

If subjects are asked to consume dietary supplements, the study must be reviewed at a convened (Full Board) IRB meeting.

For research studies involving dietary supplements, the Sponsor/Investigator is responsible for determining if the research requires an active IND. The IRB reserves the right to require additional documentation from the FDA, Sponsor, and/or Investigator regarding the product status. The proposed study may require documentation of an active IND or confirmation from the Sponsor that an IND is not required for the research.