Official Title: EEG Data Collection to Evaluate New Patient State Index Performance

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EEG Data Collection to Evaluate New Patient State Index Performance

Sponsor: Masimo
52 Discovery
Irvine, California 92618

Principal Investigator: Michael A.E. Ramsay, MD, FRCA

Study Devices:
Masimo SedLine® Brain Function Monitoring patient modules and sensors
Masimo Radical-7 monitoring devices
Masimo Root® Patient Monitoring and Connectivity Platform
Masimo SET® Pulse Oximetry sensors
[redacted] software equipped laptops for data collection

Sponsor Protocol Number: RAMS0005

IRB: Baylor Research Institute Institutional Review Board
3310 Live Oak, Suite 501
Dallas, TX 75204

Principal Investigator	Title	Signature	Date
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Sponsor	**Title**	**Signature**	**Date**
Vikram Ramakanth	Senior Clinical Program Manager		

1 INTRODUCTION

This document is a clinical investigations plan (CIP) for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with all stipulations of this plan, the conditions of IRB approval, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidelines ICH E6 GCP.

1.1 Background and Rationale

The SedLine EEG monitor (Masimo Corporation, Irvine, CA) computes the following parameters: the Patient State Index (PSI) that is calculated via 4 channels of high resolution EEG data, EMG activity, and percent of EEG suppression.

Unlike most other non-invasive patient monitoring parameters, there is no gold standard or reference against which the SedLine/Patient State Index (PSI) could be compared. Hence, to evaluate performance of two algorithms, historically clinical outcome parameters such as post-surgery wake-up time, amount of anesthesia used, and frequency of somatic events were compared to evaluate algorithm performance.

The new (investigational) PSI is similar to the current (FDA-approved) PSI but has new features to compute PSI. The data collection study and methodology as described in this plan forms the basis for evaluating performance of the new (investigational) PSI against the current (FDA approved) PSI.

1.2 Study Devices

The FDA-cleared Masimo SedLine brain function monitor is indicated for use in the operating room (OR), intensive care unit (ICU), and clinical research laboratory. It is intended to monitor the state of the brain by real-time data acquisition and processing of electroencephalograph (EEG) signals. The system includes the Patient State Index (PSI™), a proprietary computed EEG variable that is related to the effect of anesthetic agents.

The Masimo Radical-7s and Root™ Rainbow Technology Multi-Function Docking Stations are indicated for the continuous non-invasive monitoring of Oxygen Saturation (SpO2), Pulse Rate (PR), Perfusion Index (PI), Pleth Variability Index (PVI), and either FDA-cleared PSI (Rev 1.x) or investigational PSI (Rev 2.x).

2 STUDY DESIGN AND OBJECTIVES

This is a prospective, single-center study with a total enrollment of up to 150 subjects.

2.1 Specific Aims

Aim One: to collect raw and processed EEG data with Masimo SedLine monitor while anesthesiologist is blinded to the PSI (Patient State Index) score and to the raw EEG waveforms from the Masimo SedLine monitor in order to establish a Baseline for Standard Practice.

Aim Two: to collect raw and processed EEG data with Masimo SedLine monitor while anesthesiologist is monitoring subject using the current (FDA approved) PSI to supplement Standard of Care (SOC) procedures in managing anesthesia.

Aim Three: to collect raw and processed EEG data with Masimo SedLine monitor while anesthesiologist is monitoring subjects using the new (investigational) PSI to supplement Standard of Care (SOC) procedures in managing anesthesia.

Aim Four: to evaluate the performance of the new (investigational) PSI compared to current (FDA approved) PSI. Comparison measures include frequency of somatic events, total anesthesia drug used, wake up times, PSI versus Observer's Assessment of Alertness/Sedation (OAA/S).

2.2 Subjects will be assigned to one of three cohorts:

- Cohort 1: The anesthesiologist will be blinded to the PSI score and the raw EEG data. Anesthetic management in be in accordance with SOC protocols and procedures.
- Cohort 2: The anesthesiologist will be monitoring subjects using the FDA-cleared PSI Rev 1.X.
- Cohort 3: The anesthesiologist will be monitoring subjects using the investigational PSI Rev 2.X.

3 CLINICAL TEST SITE

Baylor University Medical Center

Webb Roberts Hospital

3500 Gaston Avenue

Dallas, TX 75246

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Number of Subjects

Up to 150 subjects undergoing general surgery may be enrolled into this study. Up to 50 subjects may be enrolled per Cohort.

4.2 Inclusion Criteria

- 18 years of age or older
- ASA status of I, II, and III
- Subjects undergoing general surgery
- Neurologically intact patients (e.g. no history or presence of traumatic brain injuries, neurological diseases, etc.)

4.3 Exclusion Criteria

- Subjects with any deformities, diseases or for any other reason that may prevent proper fit and application of the SedLine sensors.
- Inability to obtain subjects' physiological, vital, demographics, and real time anesthesia data.
- Subjects who are pregnant.
- Known history of drug abuse.
- Subjects deemed not suitable for study at the discretion of the Principal Investigator.

4.4 Study Timelines

Each individual patient will participate in one study visit. Each study visit may start only after the informed consent has been signed by the participant. The study visit will end in the OR upon patient wake up from anesthesia, at which point data collection is considered complete.

4.5 Subject Recruitment and Screening

Following identification of a potential subject, the patient will be approached by the principal investigator or a designated research staff member, who will explain the purpose and procedures of the study. If the patient express interest in participating in the study, they will be asked to read the written Informed Consent Form in English or Spanish depending on the patient's language preference.

All items of the Informed Consent will be explained in a way that is easily understandable, for either English or Spanish speaking subjects. The patient will be given adequate time to read through the Informed Consent, and they will be given adequate time and privacy to consider the decision of whether or not to sign the Informed Consent Form. Once all of the

patient's questions have been answered and the Informed Consent Form signed, the patient is now adequately consented. Now the patient will be enrolled as a study subject, at which time the subject will be assigned a study identification number or enrollment number.

All subjects will have their medical history reviewed at the time of screening by either the PI or the study staff who is delegated for this task. Subjects will be evaluated based on the inclusion and exclusion criteria to determine eligibility to be enrolled into the study. If a subject is deemed ineligible after screening, the subject will be withdrawn from the study.

Information regarding the subject's demographic (including, but not limited to age, weight, race, ethnicity, comorbidities, medications, etc.), preexisting allergies, skin abnormalities, and other preexisting diseases/conditions that may be relevant to the study will be recorded within a paper-based Case Report Form (CRF).

HIPAA

The pre-screening of patients will require the investigators to access personal health information to identify prospective subjects without HIPAA authorization prior to obtaining written informed consent for the study. Informed consent and HIPAA authorization will be obtained during recruitment and screening procedures as described in previous sections of this clinical investigation plan; however, pre-screening process would require a waiver of HIPAA authorization, as the research study could not be practicably carried out without this implied waiver of consent. The participants' rights and welfare will not be adversely affected by waiving consent. Patients' protected health information (PHI) will not be inappropriately reused or disclosed to any other person or entity. To further safeguard all protected health information, the data collected during the study will not be labeled with any personal identifying information, or with a code that this research team can link to personal identifying information. The data will not be stored with any protected health information identifiers.

4.6 Withdrawal of Subjects

Informed consent discussions will explicitly include emphasis that neither patient enrollment nor patient withdrawal from the study will result in any alterations to the standard clinical care. Subjects may elect to withdraw at any time up to the induction of general anesthesia.

5 STUDY DEVICE

Investigational Devices:

- Masimo new/investigational Patient State Index (PSI).

FDA-cleared Devices:

- Masimo Radical-7 and Root™ Rainbow Technology Multi-Function Docking Station (Masimo Corp) equipped Oxygen Saturation (SpO2), Pulse Rate (PR), Perfusion Index (PI), Pleth Variability Index (PVI), and current/FDA approved Patient State Index (PSI).
- SedLine patient modules, cables, and sensors.
- Masimo SET Pulse Oximetry sensors.
- Laptop computer with data collection software [redacted]

5.1 Device Accountability

5.1.1 Receipt of Study Device

Upon receipt of the of the study device supplies, an inventory must be performed and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment

will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

5.1.2 Use of Study Device

Use of devices and sensors will be documented on case report forms for each subject.

5.1.3 Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices and sensors shipped, devices/sensors used, and devices/sensors remaining. This reconciliation will be logged on the device accountability log. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed on site will only be upon written instruction from the sponsor and will be documented in the study files.

6 STUDY PROCEDURES

6.1 Cohort Enrollment

Each cohort will enroll up to 50 subjects each. Subjects will be assigned to Cohort 1 until up to 50 subjects have been enrolled, after which subjects will be enrolled to Cohort 2. Cohort 2 will enroll up to 50 subjects, after which subjects will be enrolled to Cohort 3, which will enroll up to 50 subjects. All Cohorts will have equal sample sizes.

6.2 Non-invasive readings

6.2.1 Subjects will be fitted with Masimo SedLine sensors per manufacturer's Directions for Use (DFU).

6.2.2 Subjects will be fitted with Masimo pulse oximetry sensors with Masimo SET per manufacturer's DFU.

6.2.3 The following non-invasive readings will be recorded for each study subject using the aforementioned sensors connected to Masimo Radical-7 and Root devices.

- Raw and processed EEG data, and the appropriate PSI parameter with Masimo SedLine
- SpO2, Pulse Rate, Perfusion Index (PI), and Pleth (PVI) with Masimo SET pulse oximetry

6.2.4 Observer's Assessment of Alertness/Sedation (OAA/S) will be assessed and recorded at regular intervals.

6.2.5 TIVA pump and/or bolus IV administration of anesthetic drugs will be recorded.

6.2.6 Inspired and end tidal anesthetic gas data will be recorded.

6.2.7 Where possible, the non-invasive data will be collected and stored continuously [redacted] All other data not collected via continuous, automated data collection methods will be entered on to the paper Case Report Form (CRF).

6.2.8 Comparison measures including but not limited to somatic events, total anesthesia drug used, wakeup times, OAA/S scores and a review of the raw EEG data will be used to evaluate PSI algorithms.

6.3 Cohort 1

6.3.1 Raw data from all the study sensors will be collected as described in Section 6.2 (Non-invasive readings).

6.3.2 The anesthesiologist and/or anesthesia providers will be blinded to the PSI score and the raw EEG waveform. Anesthesia management will be in accordance with standard of care (SOC) practice.

6.3.3 All clinical interventions will be based on the institution's standard of care practices.

6.3.4 All study data as described in this Clinical Investigation Plan will be provided to Masimo and analyzed.

6.3.5 Raw EEG data may be retrospectively processed by candidate PSI algorithms.

6.4 Cohort 2

6.4.1 Raw data from all the study sensors will be collected as described in Section 6.2 (Non-invasive readings).

6.4.2 The anesthesiologist and/or anesthesia providers will be able to monitor and use FDA-cleared PSI Rev 1.X to supplement SOC procedures in managing anesthesia.

6.4.3 All study data as described in this Clinical Investigation Plan will be provided to Masimo and analyzed.

6.5 Cohort 3

6.5.1 Raw data from all the study sensors will be collected as described in Section 6.2 (Non-invasive readings).

6.5.2 The anesthesiologist and/or anesthesia providers will be able to monitor and use the investigational PSI Rev 2.X to supplement SOC procedures in managing anesthesia.

6.5.3 At the anesthesiologist's and/or anesthesia providers' discretion, he/she can discontinue his/her reliance on PSI and can revert to standard of care anesthesia procedures at any time to safeguard subject health, safety, and welfare.

6.5.4 All study data as described in this Clinical Investigation Plan will be provided to Masimo and analyzed.

7 SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

In a two sample t-test, such as in this case when two different Cohorts (experimental vs. control) are being compared, the desired statistical power is usually set at 0.80. This convention implies a four-to-one tradeoff between β and α (β is the probability of a Type II error (false negatives), and α is the probability of a Type I error (false positives); 0.2 and 0.05 are conventional values for β and α, respectively). The Cohen's d value, which is the expected difference between the means of the experimental group and the control group divided by the expected standard deviation, is usually set at 0.80. Assuming that experimental and control groups have equal sample sizes, and assuming that both groups have normal distributions, this combination of statistical power and Cohen's d yields an estimated sample size of 26 samples per Cohort/group.

The current clinical Investigation plan defines enrollment of up to 50 subjects per Cohort, which would provide more than enough samples per Cohort to detect a difference between the outcome variables of the different Cohorts.

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, and unanticipated adverse device effect are provided below (ISO 14155:2011, 21 CFR 812.3(s)).

- Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
- Adverse Device Effect (ADE): an adverse device effect is any untoward or unintended response to a medical device which may result from insufficiencies in the instructions for use or deployment of the device, or from use error.
- Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a

congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.

- Serious Adverse Device Effect (SADE): a serious adverse device effect is an adverse device effect that results in death, inpatient hospitalization, severe or permanent disability or is life threatening.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life threatening problem or death cause by or associated with, a device, if the effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan, or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects. Refer to the Device Risk Analysis and Risk Assessment section for details on anticipated adverse device effects.

8.2 Anticipated Adverse Events:

Mild allergic reaction to sensor material and adhesives.

Redness or skin irritation from sensor material and adhesives.

8.3 Adverse Event Reporting:

- All Adverse Events, both Anticipated and Unanticipated, must be recorded in the CRF and recorded in detail in the Adverse Event Report Form.
- All Adverse Events must be promptly reported to the Sponsor.
- All Unanticipated Adverse Device Effects will be also reported to both the Sponsor and the IRB.
- Both Serious Adverse Events and Unanticipated Adverse Device Effects must be reported to the Sponsor within 48 hours. All other Adverse Events should be reported to the Sponsor within 5 business days.
- All Serious Adverse Events will be also reported to the IRB per IRB reporting requirements. These reports may include, but will not be limited to: date of onset; brief description of the events; their treatment; whether they resulted in death, inpatient hospitalization, severe or permanent disability or were life threatening; their relationship to the study device; and resolution.

Deviations from the study protocol

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Withdrawal of IRB approval

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

9 DATA MANAGEMENT

9.1 Provisions to Protect the Privacy Interests of Subjects

Potential study candidates will be identified following a review of the elective surgical schedule. The attending surgeon will then be contacted to confirm the appropriateness of the patient and identify any steps that are indicated to protect the subjects' privacy interests. Patient recruitment and informed consent will be obtained when there is sufficient time for a complete discussion between the investigator and the patient. Recruitment will be by direct discussion between the prospective candidates and the study investigators prior to their scheduled surgical procedure. The investigators and/or designated study staff will provide the consent form in person and give the prospective subject sufficient time to review the consent form and discuss the study with friends and family.

9.2 Data Management and Confidentiality

All documents associated with this protocol will be kept in the locked offices or on password protected computers. All data will be de-identified before any statistical analysis. Only de-identified data will be shared with Masimo for research purposes stated in this clinical investigation plan. Data collected by data capture software and data entered in case report form will be shared with Masimo via a secure, password protected server that only study staff and Masimo study team members will have access to. Blood specimens, if any are required per current clinical investigation plan, will be handled according to standard procedures for biological materials. Data will be retained for up to 2 years following completion of the final analysis.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, and copies or transcriptions certified after verification as being accurate and complete.

9.4 Screening and Enrollment Logs

A subject screening and enrollment log will be provided to study site by sponsor, and maintained by study site. The screening and enrollment log will document, at a minimum, information such as the number of subjects approached for informed consent, the date of consent, subject eligibility, subject enrollment status, subject withdraw (if applicable) and reason(s) for withdrawal.

9.5 Case Report Forms

9.5.1 The Sponsor shall provide a Case Report Form (CRF) template to the Site. The Site shall capture study data in the CRFs for each subject enrolled. The CRFs will be reviewed and signed by principal investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, it is highly recommended that the reason(s) be noted on the CRF. Case report forms are to be completed on an ongoing basis. CRF entries and corrections will only be performed by study site staffs that are authorized by the investigator. Entries and corrections to the CRF will be made following Good Documentation Practices.

9.5.2 The CRF will include the following information, including but not limited to: inclusion / exclusion criteria, whether patient consent obtained before start of study, demographic information, event timing, anesthetic drugs used and dosage, patient skin condition after sensor removal, etc.

9.5.3 The CRF will be signed by the PI, and securely transferred to Masimo in pdf format.

9.5.4 CRF entries will be checked by Sponsor personnel after receipt and any errors or inconsistencies will be queried to the site on an ongoing basis. Query resolution will be assessed and confirmed by study monitor during site visit.

9.6 Data Transfer and Storage

9.6.1 Device data will be captured through data capture software [redacted] and stored on a laptop. Device data along with a pdf copy of the CRF will be uploaded to sponsor via secure FTP portal after each study visit completion.

9.6.2 Only authorized sponsor personnel will have access to the uploaded data on the secure FTP portal, and will move it to a secure and backed-up drive at Masimo after receiving the upload from study site.

9.6.3 Device data and pdf copies of CRFs will be checked for completeness. If there are inconsistent or missing data points, a data query list will be generated and submitted to the site for corrections. [redacted]

9.7 Data Analysis

Data analysis is to be done by Sponsor personnel upon completion of study. Data analysis may include descriptive statistics, regression testing and measures of accuracy (e.g., bias, precision and root mean square of the differences).

Different sets of comparisons could be made between the three Cohorts; data for Cohorts 2 and 3 may be compared against each other, and data for Cohort 2 and Cohort 3 may be compared individually against data for Cohort 1.

9.8 Record Retention

Study data will be retained for the necessary period of time as required by the institution's regulations. Study Records shall be retained for a minimum of two years after study closure. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

10 MONITORING PLAN

10.1 As the sponsor of this clinical investigation, Masimo Corporation is required by 21 CFR, Part 812, of the Food and Drug Administration regulations to monitor and oversee the progress of the investigation. The monitor(s) assigned by Masimo Corporation to this task will be employee(s) from the Clinical Research department who are trained on departmental SOPs and have adequate experience in conducting monitoring visits.

10.2 In accordance with good clinical practices guidelines, there will be at least three scheduled monitoring visits to ensure overall regulatory compliance of the study:

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment.
- At least one monitoring visit during enrollment, preferably when enrollment has reached 10% of subjects, and then at least once every year thereafter.
- A final close out visit after the last patient had finished the study.

10.3 Study monitor(s) will initiate contact and setup on-site visits with the investigator. Study monitor(s) will be allowed, on request, access to all source documents needed to verify the entries in the CRFs and to all other GCP-related documents (IRB approvals, IRB correspondences, and ICFs) provided that subject confidentiality is maintained in agreement with HIPAA regulations.

10.4 It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency and accuracy of the data being entered on them.

10.5 During each visit, the monitor will also verify presence of informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs/SADEs and protocol deviations/violations, and check CRF against source documentation.

10.6 After each visit, the monitor will provide a monitoring report to the investigator within 4 weeks of visit completion. The monitoring report will detail findings and open action items observed during the visit. It is the responsibility of the Principal Investigator and Study Coordinator(s) to respond to the findings of the monitoring report, and complete any open action items as soon as possible but no later than 60 days of receiving the monitoring report. Any open action items not completed within the time allowed may be sufficient grounds for study site suspension or termination; it will be up to the sponsor to determine whether any incomplete action items are sufficient grounds for suspension or termination. See Section 13 for details on suspension and termination.

10.7 Depending on the quality of the data and/or changes to factors affecting patient safety, additional monitoring visits may be necessary at the sponsor's discretion.

11 PATIENT AND DATA SAFETY MONITORING AND REPORTING

No monitoring by a data and safety monitoring board is planned. Standard of care anesthesia procedures will be in place for all cohorts, thus no additional risk is presented to subjects for participation in the study.

12 BENEFITS / RISK ANALYSIS

12.1 There is no specific benefit to the individual subjects for participation in this research protocol.

12.2 The Masimo Radical-7 and Root devices, in addition to SedLine and Pulse Oximetry sensors are non-significant risk devices, and are currently FDA cleared to be used together in Adults.

12.3 The new (investigational) PSI algorithm is similar to the current (FDA approved) PSI algorithm but has new features to compute PSI.

12.4 Risks from all Masimo sensors are minimal since they are non-invasive and use biocompatible adhesives to adhere to the skin. The Masimo Radical-7 and Root monitor and accessories are non-significant risk (NSR) devices because they do not present a potential for serious risk to health, safety, or welfare of a subject and:

- The devices are non-invasive monitoring devices (not an implant); or
- The devices are not used in supporting or sustaining human life; or
- The devices are not used in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; or
- The devices do not present a potential for serious risk to the health, safety, or welfare of the subject.

12.5 Risks from Pulse Oximetry sensors: pulse oximetry sensors function by shining light through the fingers or toes of the patient in order to detect pulsation in the capillaries. These sensors are non-invasive due to their use of optical technology. As such they present minimal risk to the patient.

12.6 Risks from SedLine sensors: SedLine sensors are similarly to traditional EEG or EKG electrodes, they function by detecting electrical current naturally occurring in the human body. Just like traditional EEG and EKG electrodes, SedLine sensors are non-invasive and present minimal risk to the patient.

12.7 All patient-contact materials, including the adhesive used in Masimo sensors have undergone biocompatibility testing by original materials manufacturer.

12.8 Risks and Mitigations are detailed in the Investigator's Brochure (IB). Principal Investigator is responsible for reviewing and understanding the IB, and he/she is responsible for the training of all study staff in order to mitigate said risks.

13 ADMINISTRATIVE ASPECTS

13.1 Confidentiality

All data collected will be kept confidential and de-identified. It can only be accessed by site staff assigned to the study and authorized sponsor personnel. All data collected will be used for research purposes only.

13.2 Protocol Amendments

Any changes made to the clinical investigational plan/study protocol will be documented by way of an amendment. Before submitting protocol amendment to the IRB, the protocol amendment must be agreed upon and signed by both the principal investigator and the sponsor. The protocol amendment will be submitted to the IRB for approval. At a minimum, a clean version of the new protocol amendment will be kept on file by the PI and the sponsor, but it is recommended to keep both a clean copy and a redline copy of the protocol amendment. Protocol amendments will need to be version controlled. Both PI and sponsor will retain the IRB approval letter as confirmation that the protocol amendment was approved.

13.3 Suspension or Termination of Study Site

The sponsor can suspend or prematurely terminate the PI's and study site's participation in the study, particularly if sponsor finds serious non-compliance by the PI or site, and if such non-compliance was not resolved in a timely manner. The sponsor will document the decision to suspend or terminate the investigation in writing. A suspended study site cannot enroll new subjects.

If the sponsor determine that the study site's compliance to be inadequate at any point during the study, and sponsor move to suspend or terminate the study site, the sponsor will provide notification in writing to the principal investigator and IRB as necessary. The study site is eligible for reinstatement upon correction of any findings and any open action items prior to the suspension, and provides a written guarantee that the same non-compliance will not reoccur in the future. Site can only resume patient enrollment upon receiving written notification of reinstatement from the sponsor.

If for any GCP and Regulatory non-compliance reasons the study site is prematurely terminated by the sponsor, then the study site is not eligible for reinstatement under the same Clinical Investigational Plan/Study Protocol.

13.4 Termination of Clinical Investigation/Study due to UADE

The clinical investigation may be terminated if sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the subjects. Termination shall occur no later than 5 working days after the sponsor makes this determination, and no later than 15 working days after the sponsor first received notice of the effect.

The sponsor may resume the terminated clinical investigation with prior IRB approval if the device is non-significant risk.

14 AGREEMENT BETWEEN INVESTIGATOR AND SPONSOR REGARDING RESPONSIBILITIES FOR GOOD CLINICAL PRACTICE

International Conference of Harmonization (ICH) E6 Good Clinical Practice guidance is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

It specifies general requirements intended to:

- Protect the rights, safety and well-being of human subjects,
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- Assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

The Principal Investigator of the clinical investigation shall:

- Obtain and maintain IRB approval of the study.
- Ensure all subjects are consented prior to enrollment, per FDA Code of Federal Regulations titled 21 CFR 50.
- Ensure only appropriately trained personnel will be involved in clinical investigation.
- Maintain study records mentioned in the CIP.
- Maintain logs for study team delegation, site visit/monitoring, equipment disposition, study team training, subject recruitment and enrollment.
- Evaluate all adverse events and adverse device effects and determining whether the study is safe to continue.
- Allow the sponsor to conduct periodic monitoring of study activities to ensure GCP compliance.
- Not promote device prior to clearance by FDA for commercial distribution, except for academic purposes and scientific presentations.

The Sponsor shall insure existence and record of all necessary compliance documents, and will conduct monitoring visits to ensure appropriate conduct of the study.

15 DOCUMENT REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made:
1.0	May 02, 2016	Original version