Official Title: Comparison of Depth of Sedation Performance Between SedLine and Comparator Device During General Anesthesia

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Comparison of Depth of Sedation Performance between SedLine and Comparator Device during General Anesthesia

Sponsor: Masimo Corporation
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Principal Investigator: Richard L. Applegate II MD

Study Devices:
Masimo SedLine® Brain Function Monitoring patient modules
Medtronic/Covidien Bispectral Index (BIS) System
FDA-cleared 3rd party EEG/EKG sensors
Masimo Root® Patient Monitoring and Connectivity Platform

Sponsor Protocol Number: APPL0009

IRB: Office of Research
University of California, Davis
1850 Research Park Drive Suite 300
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Principal Investigator	**Title**	**Signature**	**Date**
Richard L. Applegate II MD	Chair of Anesthesiology and Pain Medicine		
Vikram Ramakanth	Director, Clinical Research	**Signature**	**Date**

1 INTRODUCTION

This document is a clinical investigational plan for a human research study. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. By participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of IRB approval, federal and local regulatory requirements, and 21 CFR 812, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidance ICH GCP.

1.1 Background and Rationale

Monitoring vital signs (pulse rate, respiratory rate, blood pressure, and temperature), respiratory, and anesthesia parameters is considered standard for managing patients during anesthesia. However, the end target organ of action for anesthetic agents (the brain) is not routinely monitored.

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.

In the last couple of decades a number of monitors (and/or indices) for monitoring depth of anesthesia were validated by examining measures of association between the index and either steady-state anesthetic concentration, and / or arousal. The performance of Bispectral index (BIS), state entropy/response entropy and the Narcotrend index has been published in a large number of adult studies. In general, no particular index has been shown to be substantially superior in these studies.

Use of brain function monitoring has been shown to improve clinical outcomes, by decreasing recovery and emergence times [1]. Although brain function monitoring has been in use for more than 15 years, it has not become a standard of care as confounding factors such as polypharmacy; low EEG power; EEG dynamics versus age; and patient temperature were not included in the original training data set. This can lead to reduced accuracy under these conditions.

Processed EEG-based monitor indexes such as BIS and Patient State Index (PSI™) have been shown to be useful in assessing brain activity during sedation and general anesthesia. Though both indices have shown predictive value in assessing levels of sedation/awareness, there has only been marginal correlation between the two [2, 3].

Previous attempts to compare the performance of BIS and PSI indices were limited to applying both sensors simultaneously on the forehead. With limited space and common sensors between two sets of devices, it was possible that some sensors were not positioned according to manufacturer's instructions. This protocol is designed to allow comparison of these 2 indices during clinical care. The inclusion of standardized clinical observations, acquisition of raw and processed physiological data, and anesthesia records used singularly or in combination will provide an opportunity to objectively evaluate the performance of the two devices under a wide range of clinical and patient conditions.

2 STUDY DESIGN & OBJECTIVES

2.1 General Design

The primary objective is to compare the performance of SedLine and the comparator's device systems during surgery. Relative accuracy of the individual depth of sedation indices will be compared.

This is a sponsored, prospective, non-blinded, non-randomized study. PSI, BIS and other supplemental data from both monitors will be collected [redacted] Additionally, raw EEG data [redacted] will be collected. This raw data can be used by experts to ascertain the true sedation patient state. Vital signs and anesthetic records may also be collected from hospital electronic medical records (EMR) to aid fair comparison between both devices.

EEG data and either of two indices (PSI/BIS) will not be used to guide clinical care or decisions. Raw data and sedation indices collected from both monitors will be used post-hoc (after surgery) to compare performance.

2.2 Study Endpoint

Primary endpoint is to compare performance of PSI and BIS indices across anesthesia range, Electromyography (EMG), Burst Suppression State and low power EEG conditions.

2.3 Target Enrollment

The target enrollment for the study is up to 150 subjects.

2.4 Study Duration

The anticipated duration of subject participation in this study will not exceed 1 visit during surgery. Total duration of the study is expected to be approximately one year.

3 CLINICAL TEST SITE

University of California Davis Medical Center
2315 Stockton Blvd, Sacramento, CA 95817

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Population Base

Subjects will be at least 18 years of age. Up to 150 adult subjects undergoing general surgery may be enrolled into this study. An interim analysis will be conducted after 30 subjects.

4.2 Inclusion Criteria

- Patients 18 years old and older at the time of consent.
- ASA status I, II, or III.
- English-speaking subjects.
- Scheduled for surgical and non-surgical procedures scheduled under general anesthesia (Common procedures include but are not restricted to tonsillectomy, adenoidectomy, urological procedures, dental rehabilitation, orthopedic procedures, biopsies, audiogram, nuclear scans, gastroscopy, colonoscopy, etc.).

4.3 Exclusion Criteria

- Any deformities or devices that may prevent application of EEG Sensor to forehead with a proper fit.
- Subjects who are developmentally delayed.
- Subjects deemed not suitable for study at the discretion of the 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 obtained. The study visit will end when patient wakes up from anesthesia, at which point data collection is considered complete.

4.5 Subject Recruitment and Screening

Patient recruitment and informed consent will be obtained in the UC Davis Medical Center (UCDMC) perioperative suite. Recruitment will be by direct discussion between the prospective candidates and the study investigators prior to their

scheduled surgical procedure. The investigators 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.

The screening of patients will require the investigators to access personal health information to identify prospective subjects without HIPAA authorization. The research could not be practicably carried out without this waiver of consent. The risk of harm from contacting the participants is greater than the risk of the study procedures. The research is of minimal risk and does not involve any procedures for which written consent is normally required outside the research setting. The participants' rights and welfare will not be adversely affected by waiving consent. This protected health information will not be inappropriately reused or disclosed to any other person or entity. To further safeguard all protected health information, the data 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 Informed Consent Process

All items of the Informed Consent will be explained in a way that is easily understandable. 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.

4.7 Early Withdrawal of Subjects

4.7.1 Withdrawal of Individual Subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences or loss of benefits to which they are otherwise entitled. Subjects may be withdrawn from the study at the discretion of the PI prior to expected completion for reasons such as safety concerns, failure to adhere to protocol requirements, subject consent withdrawal, etc.

Any data collected until the time of subject withdrawal may be included in the final data analysis. Information on the subject's withdrawal should be documented in the case report form and should include clear documentation of the reason for withdrawal to the Sponsor.

4.7.2 Follow-up for subjects withdrawn from study

None. There are no long term effects anticipated from participating in this study.

5 STUDY DEVICES

5.1 Description

FDA-Cleared Devices

- FDA-cleared Root™ Rainbow Technology Multi-Function Docking Station (Masimo Corporation)
- FDA-cleared SedLine patient modules (Masimo Corporation)
- FDA-cleared Bispectral Index (BIS) system (Medtronic/Covidien)
- FDA-cleared 3rd party EEG/EKG sensors (such as Covidien Kendall Kittycat electrodes or equivalent)

Data Acquisition Systems

[redacted]

5.1.1 Receipt of Study Device

Masimo may ship or hand-carry devices and sensors to the investigative sites. Upon receipt of the study device supplies, an inventory must be performed and the Equipment Shipment Check Form (FRM-2713) and the device accountability log will be completed for each device and signed by the receiver. 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 (CRF) for each subject. Any unused devices must be returned to the Sponsor at the end of the study.

5.1.3 Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices. 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.

5.1.4 Device Deficiencies

Device deficiencies are defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Record all device deficiencies on the case report form and report to the Sponsor.

5.2 Risk/Benefits

Benefits: There will be no direct benefits to the enrolled subjects. Future benefits to subjects might include continuous monitoring of patients level of sedation and sleep state sleep quality and an additional tool for determining patients mental status.

Device risks: All devices used in the study are FDA-cleared. The devices are non-invasive and present minimal risk to the enrolled subjects.
Sensor risks: 3rd party EEG/EKG function by detecting electrical current naturally occurring in the human body. These sensors are non-invasive and present minimal risk to the patient.
The 3rd party EEG/EKG sensors being used as part of the system makes the system non-defibrillator proof. This means that in the event that a defibrillator needs to be used, all of the electrodes connected to the subject will need to be removed. Study investigators will be trained and made aware of this possible risk.

6 STUDY PROCEDURES

At any time during study procedures, the physician, anesthesiologists and/or anesthesia providers or bedside nurse, at their discretion, can discontinue study procedures and exercise clinical judgment to safeguard the subject's health, safety, and welfare. Masimo data will not be used to guide clinical care or decisions.

6.1 Sensor Placement

6.1.1 Third-party EEG/EKG sensors will be applied at locations (Appendix A-FP1, FP2, F7, F8, FPZ and AFZ) recommended by the SedLine sensor array.

6.1.2 Additional EEG/EKG sensors will be applied at BIS Sensor locations on both right and left forehead placements. There are no standardized location identifiers for BIS sensor placements except for being adjacent to the SedLine EEG sensor. [redacted]

6.1.3 In total [redacted] EEG/EKG sensors may be placed on the patient's forehead. [redacted]

6.1.4 The sensors may be applied in the pre-op area or in the OR. All sensors may be disconnected during transportation of the patient.

6.1.5 At application each sensor will be checked to make sure impedance of each of the channels is less or equal to 15 kOhms in all sensors.

6.1.6 If impedance is greater than 15 kOhms, readjust sensor(s) so that impedance drops to less than or equal to 15 kOhms.

6.1.7 If impedance is still greater than 15 kOhms, check the quality of the EEG waveform. If quality is acceptable, proceed with data collection. If quality is not acceptable, replace sensor and repeat steps 6.1.5 to 6.1.6.

6.1.8 Upon a successful impedance test, the impedance test will be turned off. [redacted]

6.2 Data Collection Protocol

6.2.1 Induction is defined as the interval between the initial administration of the anesthetic agent until the patient is deemed ready for the airway to be secured by the anesthesiologist and, if necessary, intubation, is complete.

6.2.2 The Root Monitor and the BIS system will be connected to a laptop for data recording using [redacted]

6.2.3 The exact dose and time of administration of all gases and all medications that directly or indirectly target the brain and muscles (e.g. muscle relaxants) will be recorded throughout the anesthesia and continued into the recovery period until the end of the study.

6.2.4 During induction and recovery the depth of sedation will be assessed using the Observers' Assessment of Alertness/Sedation scale (OAAS).

6.2.5 All concomitant medications given between the time the EEG sensors are applied and removed may be recorded on the CRF.

6.2.6 Information regarding the subject's demographic (including, but not limited to age, weight, race, ethnicity, etc.), skin abnormalities, preexisting diseases/conditions, events related to induction, post-induction and recovery will be recorded within a paper-based Case Report Form (CRF). PSI and BIS scores will either be recorded in the paper based CRF or obtained [redacted]

6.2.7 The subject's participation in the study may be terminated at the discretion of PI or if an adverse event is observed.

6.2.8 The data collection is considered complete 5 to 10 minutes after the patient initially opens his/her eyes during the recovery phase. At the conclusion of the study devices and data recording will be stopped, and all sensors will be removed.

7 STATISTICAL PLAN

Initial subjects may be enrolled for the purposes of protocol training/learning. Data from these initial subjects may or may not be used in the interim or final analysis. As needed, the site can be permitted to enroll up to the first 10 subjects for this purpose. Informed consent will be obtained from these subjects.

7.1 For this study, analysis of BIS and PSI will be performed under four major categories:

- BIS/PSI performance across anesthesia range (Drug Response)
- BIS/PSI performance during EMG (Electromyogram)
- BIS/PSI performance during Burst Suppression State
- BIS/PSI performance during low power EEG from aging brain [4] (70-90 years)

7.1.1 BIS/PSI performance across anesthesia range:

- Total duration of incorrect index reporting for various anesthetic drugs such as GABAergic drugs and Nitrous Oxide, and levels using raw EEG data as reference to estimate appropriate clinical sedation levels.
- Total instances in which the index would have provided incorrect clinical guidance leading to more or less anesthetic agent administration.
    - Episodes of clinical “arousal events” during anesthesia as indicated by increase in heart rate and/or blood pressure by at least 20% will be noted with time entry and comment for later comparison to index. Anesthetic agent administration at the time of the “arousal event” will be noted as end-tidal inhaled anesthetic concentration or intravenous drug and administration rate as appropriate to the anesthetic administered.
    - Episodes of suspected clinical “deep anesthesia events” during anesthesia as indicated by decrease in heart rate and/or blood pressure of at least 20%will be noted with time entry and comment for later comparison to index. Anesthetic agent administration at the time of the “deep anesthesia event” will be noted as end-tidal inhaled anesthetic concentration or intravenous drug and administration rate as appropriate to the anesthetic administered.
    - The number of “arousal events” and “deep anesthesia events” per patient will be entered for each patient

7.1.2 BIS/PSI performance during EMG (Electromyogram)

- To measure the influence of EMG on calculation of sedation index, correlate changes in sedation index with OAAS or surgical stress known to the anesthesiologist.
- Frequency of false positive and false negative instances of “arousal events”.

7.1.3 BIS/PSI performance during Burst Suppression State

- Frequency of false positive and false negative burst suppression detection for each patient. Overall accuracy will be calculated across all patients. Raw EEG data would be the reference to determine the presence/absence of burst suppression.
- Instances of incorrect sedation index values during burst suppression state.

7.1.4 BIS/PSI performance during low power EEG from aging brain (70-90 years)

- Similar and relevant analysis will be performed as stated in section 7.1.1.

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.
- Discomfort, redness or skin irritation.

8.3 Adverse Event Reporting:

- All Adverse Events, both Anticipated and Unanticipated, must be recorded in the within the CRF and 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.

8.4 Deviations from the study protocol

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated with the exception that under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor or the IRB. 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 documented and 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. If protocol deviations continue to occur frequently at a study site, a corrective and preventive action (CAPA) may be opened by the Sponsor.

8.5 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 VULNERABLE POPULATIONS

9.1 Definition

Vulnerable populations are defined as disadvantaged sub-segment of the community requiring utmost care, special considerations and protections in research. This study will recruit subjects from the following: economically disadvantaged or unemployed and educationally disadvantaged.

9.2 Protection of vulnerable subjects

- There is no compensation provided to eliminate possibility of undue influence due to financial incentive for economically disadvantaged subjects.
- Educationally disadvantaged subjects will be provided ample time to ask questions and comprehend information.
- Medical care will be provided to these subjects if they are injured as a direct result of participating in this research study. The cost of treatment for any research related injury will be covered by Masimo.

9.3 Responsible Parties

- The IRB will review research with vulnerable populations and evaluate consent, level of risk, coercion, and the reason for choosing this particular subject population. The IRB will be responsible for determining what practices will include continuing review for compliance while monitoring these studies.
- The Investigator holds the ultimate responsibility for protecting the rights, safety, and welfare of research subjects by ensuring that all regulations and proper documentation of consent is handled in a compliant and timely manner.

10 DATA MANAGEMENT

10.1 Confidentiality of Records

Information about the patients will be kept confidential. The data will be stored on a password protected database on a secure server, accessible only to the Investigators. Study data that will be released to Masimo and other regulatory authorities will be de-identified and will only pertain to study data collection such as EMR and anesthesia records, demographics, events during pre-induction, induction and recovery, and the recordings from the EEG/EKG sensors.

10.2 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. For this study, the case report forms may also be used as source worksheets.

10.3 Case Report Forms

The Site shall capture study data in the CRFs for each subject enrolled. The CRFs will be completed and initial and dated by the PI or delegated personnel. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must 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 staff, authorized by the investigator. Entries and corrections to the CRF will be made following Good Documentation Practices.

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, device readings, and if occurrence of any adverse event,

protocol deviation, and device deficiencies, etc. The CRFs will be signed by the PI to attest that the data is complete and accurate and forward a copy to Masimo.

CRF entries will be verified by study monitor and any errors or inconsistencies will be queried to the site on an ongoing basis. Any changes will be made directly on the paper CRFs and re-verified. Query resolution will be assessed and confirmed by study monitor during site visit.

10.4 Data Transfer and Storage

Training on CRF completion will be provided to study personnel prior to data collection. Original CRFs will be stored in a secure location at site. Original CRFs will be scanned and sent to sponsor. [redacted] Device data, raw EEG data, vital signs data, and anesthesia records, along with electronic copies of the CRFs will be uploaded to sponsor via secure portal after each study visit completion.

CRFs will be checked for accuracy and completeness of data. If there are inconsistent or missing data points, a data query list will be generated and submitted to the PI or designee, who shall both follow GDP practices for data correction by striking through the old entry, adding in new entry with initial and date, and resend to Masimo the corrected CRF. Once all queries have been resolved, Masimo engineers are notified that data is ready for analysis. To ensure data integrity, Masimo engineers will only have read access to study data, therefore are unable to unintentionally tamper with the original data files.

10.5 Record Retention

All study information, including but not limited to study correspondence, study logs, device accountability records, consent forms, subject records, and copies of CRFs should be maintained in the Investigator site files.

Study records shall be retained during the study and for a minimum of two years after date of study closure or date when records are not required to support 510(k) clearance. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

The Sponsor is responsible for verifying study data, retaining records, analyzing data, and authoring study reports.

11 MONITORING PLAN

11.1 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 a direct employee from the Clinical Research department trained on departmental SOPs on conduct and monitoring of sponsored studies.

11.2 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, when about 10-15% done and every 6 months thereafter.
- A final close out visit after the last patient had finished the study.

11.3 The monitor will contact and visit the investigator and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other GCP-related documents (IRB approvals, IRB correspondences, and ICFs) provided that subject confidentiality is maintained in agreement with HIPAA regulations.

11.4 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.

11.5 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.

11.6 After each visit, the monitor will provide a monitoring follow-up letter to the investigator within 4 weeks of visit completion. The monitoring follow-up letter 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 follow-up letter, and complete any open action items as soon as possible but no later than 60 days of receiving the monitoring follow-up letter. 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.

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

12 ADMINISTRATIVE ASPECTS

12.1 Protection of Human Subjects

Per 21 CFR 50, written consent must be obtained from each subject or from their legal guardian prior to any study procedures in accordance with applicable federal, state, and study site regulations. The Investigator must keep a copy of the signed consent form in each subject’s record and provide a copy to the subject as well. The Investigator shall not allow a subject to participate in a study or sign consent prior to IRB approval.

Prior to the start of data collection or subject enrollment, the Investigator must provide documentation of IRB approval of the study protocol and a copy of the approved informed consent form (21 CFR 50).

All subjects will be monitored closely throughout the study. The following measures will be taken to ensure the privacy of subjects:

- A code (unique identification) number for each subject will be kept on file.
- Only their correspondence identification number will identify subjects.
- Access to the documents and data will only be made to the Investigators and study staff in the study.
- The confidentiality of these documents will be protected to the extent provided by the law.

12.2 Institutional Review Boards

The Sponsor and/or Investigator must submit the protocol to the appropriate IRB and obtain a copy of the written and dated approval letter.

The approval letter should state the name of the documents reviewed, date of review, date of approval, and reference the study name (protocol title, study number, and version).

The informed consent used by the Investigator must be reviewed and approved by the Sponsor prior to submission to the IRB. The Investigator cannot enroll subjects until a copy of the approved informed consent is obtained from the IRB.

Any amendments to the protocol or informed consent should be submitted to the IRB for review and approval per 21 CFR 56. The IRB should be notified of any changes that may affect conduct of the study or pose safety risks to the subjects.

12.3 Confidentiality

All data collected will be kept confidential and de-identified. It can only be accessed by researchers and will be used for research purposes only.

12.4 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 for approval, the protocol amendment must be agreed upon and signed by both the Investigator and the Sponsor. The Investigator shall not make any changes to the protocol without Sponsor approval and documented approval from the IRB. Both PI and Sponsor will retain the IRB approval letter and approved protocol as confirmation that the protocol amendment was approved.

12.5 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 GCP and federal regulations 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 and/or IRB.

12.6 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 not later than 5 working days after the Sponsor makes this determination, and not 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.

13 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.

14 REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made:
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

REFERENCES

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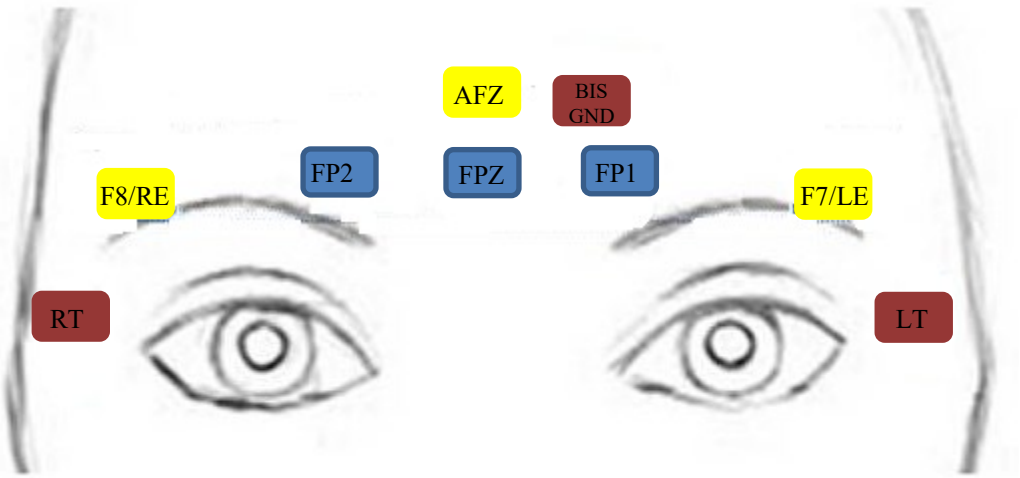
APPENDIX A: SENSOR LOCATIONS



SedLine Electrode Positions

SedLine and BIS Shared Electrode Positions

BIS Electrode Positions