Official Title: SedLine Engineering Data Collection Study in Pediatric Patients Undergoing General Anesthesia or Sedation

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SedLine Engineering Data Collection study in Pediatric Patients undergoing General Anesthesia or Sedation

Sponsor:	Masimo Corporation 52 Discovery Irvine, California 92618
Principal Investigator:	Gregory Hammer , MD
Study Devices:	Masimo SedLine® Brain Function Monitoring patient modules Masimo SedLine Pediatric sensors Masimo Radical-7 SET Pulse CO-Oximeter devices and SpO2 sensors Masimo Root® Patient Monitoring and Connectivity Platform
Sponsor Protocol Number:	HAMM0001
IRB:	Stanford IRB, Stanford University 3000 El Camino Real Five Palo Alto Square, 4th Floor Palo Alto, CA 94306

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Sponsor	**Title**	**Signature**	**Date**
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1 INTRODUCTION

This document is a clinical investigational plan for a human research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of IRB approval, federal and local regulatory requirements, the Declaration of Helsinki, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidance ICH GCP.

1.1 Background and Rationale

Anesthesia and brain monitoring in pediatric patients

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.

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 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.

EEG-based monitors 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]

All information used by these brain function monitors has been derived from adult EEG data where the difference between the EEG when awake and the EEG when anaesthetized is obvious. The EEG in awake children is well described and steadily changes with maturation, but our knowledge of the EEG during anesthesia in children is scant and at this stage too limited to make any assumptions about extrapolating adult data to children. Therefore they ought to be assessed specifically in children.

There is little, but increasing, evidence that these devices work in older children, and that in older children they may improve some outcomes.

The SedLine Monitor

The SedLine® (Masimo Corporation, Irvine, CA) technology is based on more than 15 years of technical and clinical development. The device uses a multivariate algorithm to assess the patient's EEG data from all 4 channels and determine the Patient State Index (PSI™) value as a measure of anesthetic depth. The PSI was developed as a measure of hypnosis during anesthesia delivery and is based on quantitative electroencephalogram features, recorded from anterior scalp sites, as input to a multivariate algorithm that quantifies the most probable level of hypnosis. The PSI has a range from 0 (suppression of EEG) to 100 (fully

awake), with decreasing values indicating increasing levels of hypnosis. A PSI range of 25-50 indicates an adequate hypnotic state for general anesthesia. It has been demonstrated that the PSI has a significant relation to level of hypnosis, as measured by standard scales for quantifying level of alertness and sedation during intravenous propofol anesthesia as well as during inhalation anesthesia using isoflurane, sevoflurane, and desflurane. [4]

The PSI algorithm was constructed following a systematic study of the quantitative electroencephalogram changes that accompanied loss and return of consciousness and the most probable underlying sources of those changes, leading to hypotheses about the role of cortical and subcortical structures–systems in the maintenance of the conscious state and the development of the algorithm. [4-6]

[redacted]. The sensor technology was developed to improve the acquisition of EEG signals and was used in NASA's Sleep Studies in 1998. By providing an integrated algorithm based upon 4-channels of EEG data, demonstrated reliability under challenging clinical conditions and superior resistance to cautery, the SedLine monitor system offers a cost-effective alternative to other monitors. The system is currently in use at some of the nation's leading healthcare institutions.

The SedLine Monitor consists of a SedLine Module that calculates the PSI using the EEG signals acquired from the EEG Sensor Array. A Graphical User Interface called Root displays raw EEG waveform and processed information including PSI.

SedLine® brain function monitoring for the Root™ patient monitoring platform helps improve anesthetic management by providing: a) four simultaneous EEG channels enable continuous assessment of both sides of the brain; b) a single sophisticated algorithm for Patient State Index (PSI™) about a patient's response to anesthesia; c) superior resistance to electrocautery minimizes signal drop out and d) multiple screen views expand information while enabling customization in the OR and ICU.

The SedLine module easily plugs into the Root patient monitoring platform via Masimo Open Connect™ (MOC-9™) ports.

The SedLine sensor is designed for ease in application and enhanced patient comfort while ensuring the highest quality data. Four active leads collect higher volume of data in key areas of frontal lobe. The sensor was designed for quick and easy application.

Since EEG data recording in pediatric patients under anesthesia and sedation is limited, we intend to collect high resolution EEG data using a SedLine Monitor in pediatric patients and over a wide range of anesthetics. Additionally, in order to assess the impact of anesthetic drug administration on vital sign parameters routinely used during anesthesia, we intend to collect other noninvasive parametric data including blood pressure, temperature, oxygen saturation and respiratory rate. Blood pressure and temperature will be recorded from the hospital's standard of care devices, while oxygen saturation and respiratory rate will be collected using Masimo Rainbow® Pulse CO-Oximeter devices. Masimo Rainbow® is a noninvasive monitoring platform enabling the assessment of a wide range of blood constituents and physiologic parameters such as total hemoglobin (SpHb), Oxygen Saturation (SpO2), Pulse Rate (PR), Perfusion Index (PI).

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 current and future SedLine/Brain function monitoring algorithms under a wide range of clinical and patient conditions. It will also address limitations with collecting these data during sedation and general anesthesia.

Masimo's SedLine monitor is FDA cleared, noninvasive and is considered to be non-significant risk. Masimo Pulse CO-Oximeter sensors and devices are FDA cleared and considered to be non-significant risk as well. The SedLine Pediatric sensor is an investigational device that is being developed for pediatric use. The SedLine Pediatric sensor uses the same materials and intended use as the FDA-cleared SedLine adult sensor.

1.2 Study Devices

- FDA-cleared Radical-7 and Root™ Rainbow Technology Multi-Function Docking Station (Masimo Corp) equipped with Patient State Index(PSI), Oxygen Saturation, Pulse Rate, and Perfusion Index.
- FDA-cleared SedLine patient modules
- Investigational SedLine forehead EEG sensors for pediatric use
- Masimo SET Pulse CO-Oximeter sensors (optional)
- Cables for use with Radical-7 and Root devices
- Laptop computer with [redacted] Automatic Data Collection (ADC) (data collection software)

2 STUDY DESIGN AND OBJECTIVES

The primary objective is to collect SedLine EEG data along with head size measurements, vital signs, patient demographics, anesthetic record and surgical procedure data during general anesthesia or sedation. There are no endpoints of this study as data collection will be used for product development.

Data will also be collected using the SedLine array or KittyCat electrodes in order to collect EEG data on the younger pediatric population along with head size measurements, vital signs, anesthetic record and surgical procedure during general anesthesia or sedation for product development.

3 CLINICAL TEST SITE

Lucile Packard Children's Hospital

725 Welch Road

Palo Alto, CA 94304

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Number of Subjects

Up to 220 pediatric subjects undergoing general surgery may be enrolled into this study. Up to 120 subjects will be enrolled between age 12 months and 17 years and up to 100 subjects with ages less than 12 months.

4.2 Inclusion Criteria

- Patients 17 years old and younger.
- ASA status I, II, or III.

- Scheduled for surgical and non-surgical procedures scheduled under general anesthesia or sedation (Common procedures include but are not restricted to tonsillectomy, adenoidectomy, urological procedures, dental rehabilitation, orthopedic procedures, biopsies, audiogram, nuclear scans, gastroscopy, colonoscopy, etc. Surgery can be open, laparoscopic, or robotic).

4.3 Exclusion Criteria

- Any deformities or devices that may prevent application of SedLine Array to forehead with a proper fit.
- Cases in which a rapid sequence induction is indicated (emergency, full stomach precautions).
- 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 in the PACU 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's parent or guardian 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's parent or guardian expresses interest in participating in the study, they will be asked to read the written Informed Consent Form in English or Spanish depending on their 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's parent or guardian 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 and have their child participate in the study. If the patient is within age requirements for Assent, the patient will need to read and sign the Assent Form. Once the patient's parents and guardians questions have been answered and the Informed Consent Form and Assent (if applicable) is 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 on the 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 (HIPAA authorization is included in the same form as the Informed Consent); however, pre-screening process would require the IRB to grant 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. The data will not be stored with any protected health information identifiers.

4.6 Withdrawal of Subjects

Any refusals or withdrawals from the study will be documented, with the reason recorded. The investigator or treating anesthesiologist may withdraw a patient from the protocol if it is deemed it is no longer feasible to continue the study or that the continuation of the study will affect the subject's safety and well-being.

Participants are free to withdraw from the study at any time. Parents will be informed that a refusal to take part in the study will not alter the clinical treatment of their child.

4.7 Vulnerable populations

Vulnerable populations that may be enrolled in this study include children and non-English speakers. To protect children, patients and parents/guardians will be provided with adequate time to read the informed consent and to have their questions answered. Assent forms will be provided to age-appropriate subjects as required by the IRB, and by obtaining parental/guardian permission from one parent as required by the IRB. To protect non-English speaking subjects, informed consent and assent forms in their native language will be provided. As only Spanish-speaking subjects are anticipated to be enrolled in the study, informed consents and assents in Spanish will be provided to the subjects and their parents/guardians. The site will also have Spanish speaking translators available to help verbally answer any of the subject's questions.

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.

5 STUDY DEVICES

Investigational Devices:

- Masimo SedLine Pediatric Sensor: this sensor is identical to the adult sensor in materials but has been reduced in size to fit the pediatric population.

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 adult sensors.
- Masimo SpO2 sensors (optional)
- Up to 10 Medtronic KittyCat Electrodes with leadwires

Data Acquisition

- Neuroscan EEG Data Acquisition System [redacted]
- Laptop computer with data collection software – both Automated Data Collection software (Masimo Corp) [redacted]

5.1 Device Accountability

5.1.1 Receipt of Study Device

Upon receipt of the of the study device, 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

At any time during study procedures, at the discretion of the anesthesiologists and/or anesthesia providers, they can discontinue study procedures and exercise clinical judgment to safeguard the subject's health, safety, and welfare. EEG data from the investigational SedLine pediatric sensor or KittyCat electrodes will not be used to guide clinical care or decisions. The study procedures described below are within the institution's standard of care anesthesia procedures.

6.1 Pre-Induction

The SedLine pediatric sensor array is comprised of four (4) central electrodes and two (2) lateral electrodes (See Figure 1). For subjects between 13 months and 17 years, the pediatric SedLine sensor array will be applied according to manufacturer's directions for use before premedication or start of anesthesia. Up to 4 KittyCat electrodes will be applied at BIS Sensor locations for on-label BIS XP with 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 as shown in Figure 2. Both the SedLine EEG Sensor and the additional KittyCat Electrodes are connected [redacted]

For subjects 12 months or younger, either the SedLine pediatric sensor array or the KittyCat electrodes will be applied to the subject. If the SedLine sensor is not used, 6 KittyCat electrodes may be placed in similar locations to the SedLine sensor array. An additional 4 BIS sensor placements will be optional depending on the amount of available space on the subject's forehead as determined by the PI and/or research staff. These KittyCat electrodes will be connected [redacted] the SedLine module. [redacted]

At application each lead will be checked to make sure impedance of each of SedLine channel is less or equal to [redacted] in all electrodes. Good contact is indicated by a green or yellow color on the electrode status display on Root. Upon a successful impedance test, the impedance test will be turned off. Baseline EEG will be recorded for approximately 3 minutes.

SedLine and SpO2 sensors may be placed on the subject and connected to the Radical 7 and/or Root during pre-op or before anesthesia. The SpO2 sensor's usage will be optional in this study. Data will be recording in [redacted] Automated Data Collection (ADC) software. The SedLine sensor and other sensors may be disconnected during transportation of the patient and reconnected in the operating room.

6.2 Anesthetic Protocol

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. After IV induction or inhalation (sevoflurane or propofol) induction, anesthesia will be maintained using either sevoflurane or propofol (approximately 50% of patients will be in each group).

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. All concomitant medications given between the time the EEG electrodes are applied and removed are to be recorded.

<u>Sevoflurane for Maintenance</u>

In patients receiving sevoflurane for induction and maintenance following IV catheter insertion, sevoflurane will be administered when feasible in up to 3 steps [redacted] in order to achieve a stable end-tidal sevoflurane concentration of [redacted] The order of these 3 steps will be assigned randomly prior to induction of anesthesia. In addition, nitrous oxide may be used during induction and maintenance of anesthesia, and fentanyl or remifentanil may also be used.

Step Changes is defined as the phase immediately following induction and intubation, if applicable. Sevoflurane, either with or without N2O, will be administered during step changes with no changes to either sevoflurane or N2O during the step change interval.

The anesthesiologist will increase and/or decrease the target anesthesia drug in a stepwise manner and hold for [redacted] steady state at the target age adjusted MAC for each of the following

concentrations as indicated in Table 1. Steady state is defined as the target end-tidal concentration ± 0.1% for sevoflurane. The lightest MAC step will be discontinued if signs of "light" anesthesia are observed; however, the anesthesiologist at his/her discretion may continue to collect step change data at higher target effect site concentration in accordance with the protocol.

Table 1

Target MAC (Minimum Alveolar Concentration) Step Changes		
Scheme 1	Scheme 2	Scheme 3
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 1: 1 MAC is 2.5% for children 6 months – 10 years of age, and 2% in children over the age of 10 years (from Cote CJ, Lerman J, Anderson BJ. A Practice of Anesthesia for Infants and Children , 5th ed, p. 101-2, Elsevier Saunders, Philadelphia, PA; 2013)

Whenever feasible, the maintenance anesthetic agent (sevoflurane) will be reduced at the end of the surgical procedure in a step-wise fashion, with each step at least 5 minutes in duration. Examples include sevoflurane 4% - 3% - 2% - off.

For Propofol Infusion:

In patients receiving propofol for maintenance of anesthesia, propofol will be administered when feasible in up to [redacted] in order to achieve infusion rates at approximately the following steps.

[redacted]

These step changes will be done at the discretion of the anesthesiologist caring for the patient at suitable time points during the procedure. The goal will be to capture data during a stable infusion of [redacted] in duration. Changes in the infusion rate should ideally not occur until [redacted] have passed at each step. Since the timing of these intervals will be at the discretion of the treating anesthesiologist, the order will not be randomly assigned.

6.3 Depth of Sedation

During induction and recovery the depth of sedation will be assessed using the University of Michigan Sedation Scale (UMSS).

Table 2: University of Michigan Sedation Scale

1. Awake/Alert
2. Minimally Sedated: Tired/sleepy, appropriate response to verbal conversation and/or sounds
3. Moderately Sedated: Somnolent/sleeping, easily aroused with light tactile stimulation
4. Deeply Sedated: Deep sleep, aroused only with significant physical stimulation
5. Unarousable

The UMSS is an observational tool that scores the patient's responsiveness to stimuli in a manner consistent with nationally recognized definitions and was found to have a moderate to high correlation with BIS monitoring in children under 18 years old. [7]

6.4 Maintenance of anesthesia

Anesthesia will be maintained using the standard clinical practice and at the discretion of the anesthesiologist.

6.5 Anesthesia Recovery

During recovery in the PACU, EEG and other physiological data will be collected (if patient's tolerance permits it). [redacted]. Data collection may be terminated during this time period at the PI's and/or designated research staff's discretion.

6.6 Excluded Medications and Treatments

There are no excluded medications or treatments for this study.

6.7 Measurements

EEG waveforms will be collected from the SedLine module and Neuroscan Data Acquisition System and anesthesia record with concomitant medications. Additionally, head size and vital signs such as heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation will be collected using FDA approved monitors and/or standard of care (SOC) monitors.

7 SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

The purpose of data collection is an observational study to build a database of representative PSI signal profiles for the pediatric population under select conditions. Sample size is therefore non-deterministic by normal

sampling means. Approximately 220 subjects will be enrolled in the study. Site should do its best to achieve sufficient enrollment in all age groups.

Age
12 months and younger
13-35 months
3-5 years
5-11 years
11-17 years

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.

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.

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. 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.

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 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 (Pulse-Ox Automated Data Collection and Rugloop) 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. 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 the location where data is being securely stored, therefore are unable to unintentionally tamper with the original data files.

9.7 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 6 months 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, thus no additional risk is presented to subjects for participation in the study.

12 BENEFITS / RISK ANALYSIS

Benefits: There will be no direct benefits to the enrolled subjects.

Sensor risks: SedLine sensors are similar 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. However, as with all adhesives skin irritation due to sensitive skin can still occur.

All patient-contact materials, including the adhesive used in the design of the Masimo sensors, have been subjected to biocompatibility tests per ISO 10993-1 and results demonstrate that the materials are non-toxic, non-irritating, and non-sensitizing. The sensors have been subjected to performance, mechanical, and electrical testing and results demonstrate that the sensors meet the requirements for safety and effectiveness for the intended use of the product.

The SedLine sensor incorporates Means of Protection (MOPs) to isolate patients and operators from the risks of electric shock that are consistent with the allowed leakage current limits considered safe for patients. Biocompatibility testing information for all the sensor materials that contact patient skin is available. The sensor has undergone performance, mechanical, electrical, environmental, and material requirements including, but not limited to, skin surface temperature, electromagnetic compatibility, temperature limits, ESD (electrostatic discharge) test, withstand voltage, storage temperature, and biocompatibility tests.

System risks:

The KittyCat electrodes 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 KittyCat electrodes connected to the subject will need to be removed. Study investigators will be trained and made aware of this possible risk.

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

15 APPENDIX

Figure 1: The SedLine sensor array

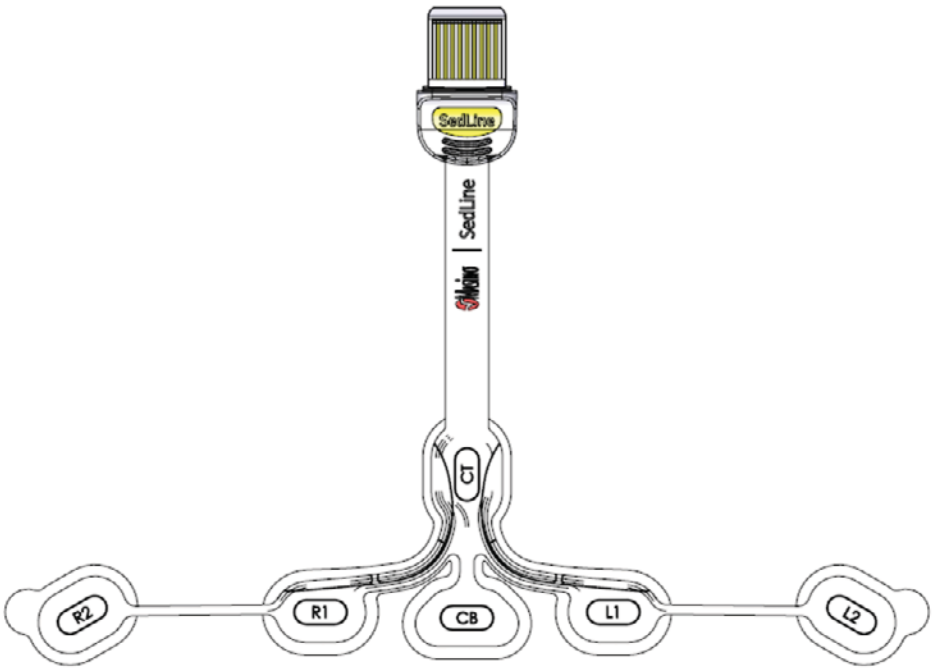
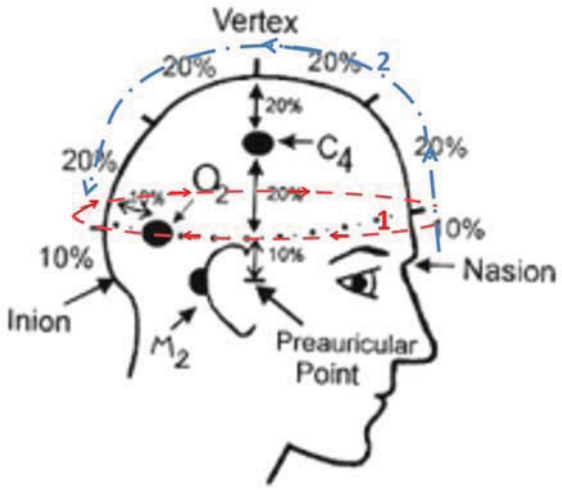


Figure 2: Sensor Locations

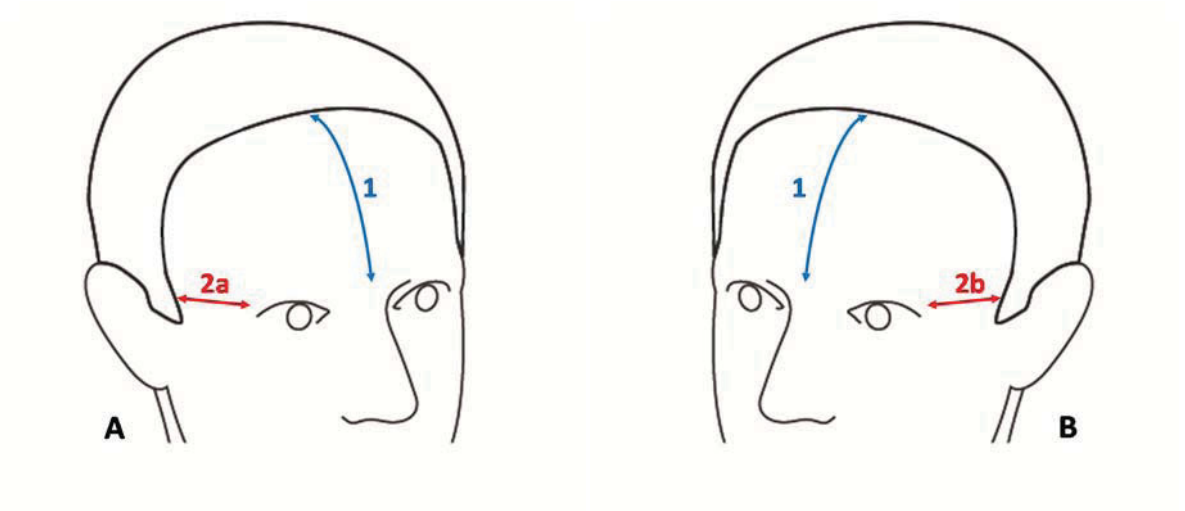
Figure 3: Head measurements



Head measurements are in centimeters and made in the following manner:

Measure and record the head circumference from a distance of approximately 10% above the Nasion to approximately 10% above Inion; as indicated by the red line in the Figure 4. Measure and record the distance from the Nasion to the Inion, a bony protuberance at the base of the skull, by following an imaginary line that bisects the crown of the head; the blue line indicates the direction of this head measurement in Figure 4.

Figure 4: Forehead measurements



Forehead measurements in centimeters: #1 (blue line) – distance from the nasion to the forehead hairline in the middle of the face/forehead. #2 (red lines) – two of the same measurements, one on each side of the head: the distance from the edge of the eyebrow to the hairline measured across the temples.

REFERENCES

1. Schneider, G., et al., EEG-based indices of anaesthesia: correlation between bispectral index and patient state index? Eur J Anaesthesiol, 2004. 21(1): p. 6-12.
2. Soehle, M., et al., Comparison between bispectral index and patient state index as measures of the electroencephalographic effects of sevoflurane. Anesthesiology, 2008. 109(5): p. 799- 805.
3. Soehle, M., et al., Patient state index vs bispectral index as measures of the electroencephalographic effects of propofol. Br J Anaesth, 2010. 105(2): p. 172-8.
4. Prichep, L.S., et al., The Patient State Index as an indicator of the level of hypnosis under general anaesthesia. Br J Anaesth, 2004. 92(3): p. 393-9.
5. John, E.R., A field theory of consciousness. Conscious Cogn, 2001. 10(2): p. 184-213.
6. Gugino, L.D., et al., Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. Br J Anaesth, 2001. 87(3): p. 421-8.
7. Malviya, S., T. Voepel-Lewis, and A.R. Tait, A comparison of observational and objective measures to differentiate depth of sedation in children from birth to 18 years of age. Anesth Analg, 2006. 102(2): p. 389-94.

16 DOCUMENT REVISION HISTORY

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