Official Title: Correlation Endoscopic View of Airway Obstruction With RRa in OSA Patients Under DEX Monitored With SedLine EEG

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Correlation of Endoscopic View of Airway Obstruction with RRa signal in OSA patients under dexmedetomidine anesthesia monitored with SedLine EEG.

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Name (Principal Investigator)	Title	Signature	Date
David Drover	Professor of Anesthesiology		

Name (Sponsor)	Title	Signature	Date
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1. INVESTIGATOR AND FACILITIES

1.1 Study Location

Stanford University Medical Center
300 Pasteur Drive
Stanford, CA 94305

Blood sample analysis laboratory
iC42 Clinical Research and Development Lab
1999 N Fitzsimons Parkway Suite 100
Aurora, CO 80045

1.2 Study Management

1.2.1 Principal Investigator (PI)

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2. BACKGROUND AND PURPOSE

Many patients diagnosed with obstructive sleep apnea (OSA) go on to have surgery for treatment of this condition. Since there can be several anatomical causes of obstruction, it can be important to determine the anatomical cause before proceeding to surgery. One technique to determine the anatomical cause is to have the patient undergo a sleep endoscopy study. During a sleep endoscopy study the patient is given medications in an attempt to simulate natural sleep as best as possible. Currently, the practice at Stanford Medical Center is to induce sleep with a dexmedetomidine (DEX) infusion with no other medications. We believe this will give us the most efficient and natural sleep as is possible in the operating room setting.

Further, EEG signal processing of DEX is an area, which is not entirely characterized, and this study allows one to collect information from subjects in a more clean method where one is essentially looking at the effects of that drug, without the multiplicity of potentially interactive effects of other anesthetic agents in effect, also.

Dexmedetomidine is primarily used in ICU and procedural sedation. It has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period. It is shown to have shorter extubation time [1]. It is associated with less delirium but depresses the heart rate. It is also shown to have reduced the amount of time spent in the ICU [2]. Dexmedetomidine (commercially Precedex) was taken off patent in 2013 and its use is expected to rise. The anesthetic effect of dexmedetomidine is different

from other popular anesthetics such as propofol and fluranes in that it induces more sleep like EEG patterns without a significant alpha frequency present. It primarily generates slow waves. It is important to study these different patterns for dexmedetomidine alone and in conjunction with Propofol and other drugs to characterize the EEG patterns.

Recent research has discovered that common anesthetic agents may have a unique EEG signal based on anesthetic class. This study presents a unique instance when sleep is induced with the single agent DEX. With the EEG continuously being recorded we will mathematically model the effect of DEX on EEG.

Many of these patients subsequently undergo induction of general anesthesia with ketamine or propofol. This will further allow us to characterize the EEG effect of ketamine and propofol. Inclusion of patients requiring DEX for sedation will be the primary inclusion criteria since that will accomplish the primary endpoints. There will be 3 types of patients based on the type of anesthesia, the sedation period, the surgical plan, and the anesthesiologist preferences. The 3 types of patients will be: 1) patients requiring DEX sedation but non-requiring subsequent general anesthesia, 2) patients requiring DEX sedation and then proceed on to propofol induction of anesthesia, and 3) patients requiring DEX sedation and then proceed on to ketamine induction of anesthesia.

Even when an anesthesiologist performs deep sedation, this physician may be remote from the airway and assessment of level of sedation and airway patency may be difficult. It is likely that prior to airway obstruction that the level of sedation may be excessive or airway obstruction may precede deep sedation. A synergism between the PSI and RRa may show the advantage of both of these monitors to protect patients against morbidity and mortality caused by airway obstruction.

The RRa Monitor

The Masimo Rainbow Acoustic Monitor (RAM) for Respiratory Rate (RRa) is cleared by the FDA and is designed to noninvasively convert acoustical airflow patterns into respiratory rate measurements. The sensor uses similar adhesives as found in other adhesive based sensors along with other biocompatible materials suitable for continuous skin contact. The bedside unit also continuously measures physiologic parameters such as oxygen saturation and pulse rate.

Masimo developed the Rainbow Acoustic Monitoring (RAM) method for respiration rate (RRa) to overcome the limitations of manual methods and existing continuous monitoring methods, thoracic impedance pneumography and capnography. Rainbow Acoustic Monitoring was designed for ease of use, high patient tolerance, and accuracy in all patient care settings. The Rainbow Acoustic Sensor detects upper airway acoustical signals produced by the turbulent airflow that occurs during both inhalation and exhalation. Figure 1 is a sample of the acoustic signal and shows several complete breaths, each one characterized by a pair of envelopes, the first during inhalation and the second during exhalation. The amplitude of the acoustic signal is related to the strength of the breath, sensor placement, and conduction of sound from the trachea through the muscle and skin in the patient's neck. The mechanical coupling of the sensor to the body surface helps separate the breathing signal from ambient background noise. Signal processing algorithms convert these acoustic patterns into breath cycles and calculate the respiration rate. Rainbow Acoustic Monitoring algorithms produce a reliable measurement by distinguishing breath patterns from other biological signals such as carotid pulses, vocalization, coughs, ambient background noise, and respiratory synchronous signals, such as snoring or wheezing. The algorithm constantly measures breath signal strength compared to background noise. When the signal falls below the minimum threshold, as could occur during shallow breathing (hypopnea), the algorithm forces the respiration rate to zero, resulting in an alarm condition. The acoustic waveform amplitude is affected by a variety of factors

preventing comparisons between patients for other physiologic determinations. However, changes in tidal volume may indicate relative physiologic changes within the same patients.

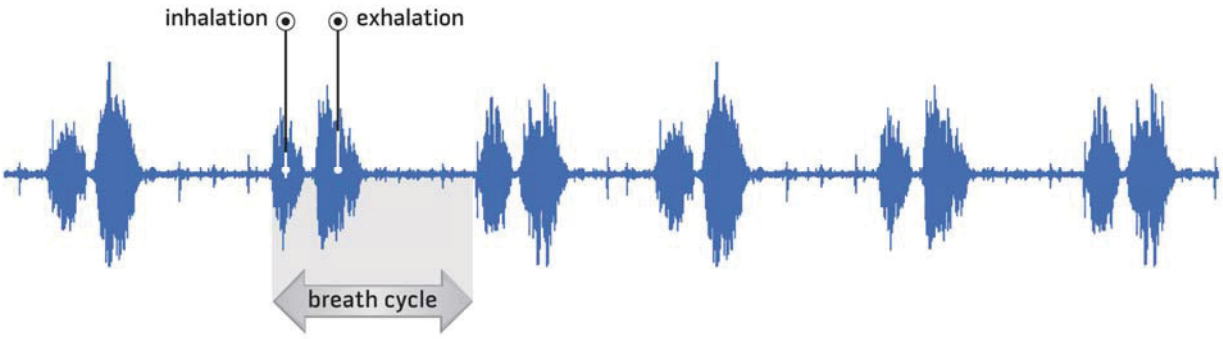

Figure 1 – Acoustic signal showing several complete breaths. Note the strength of breathing envelope in relation to the baseline environmental noise signal.

The SEDline Monitor

The SedLine® (Masimo Corporation, Irvine, CA) technology is based on more than 10 years of technical and clinical development. The device uses a sophisticated 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 (3).

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 (3-5).

[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. (Figure 2) The system is currently in use at some of the nation's leading healthcare institutions.

Figure 3: Guidelines for PSI Values.

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. (Figure 4)

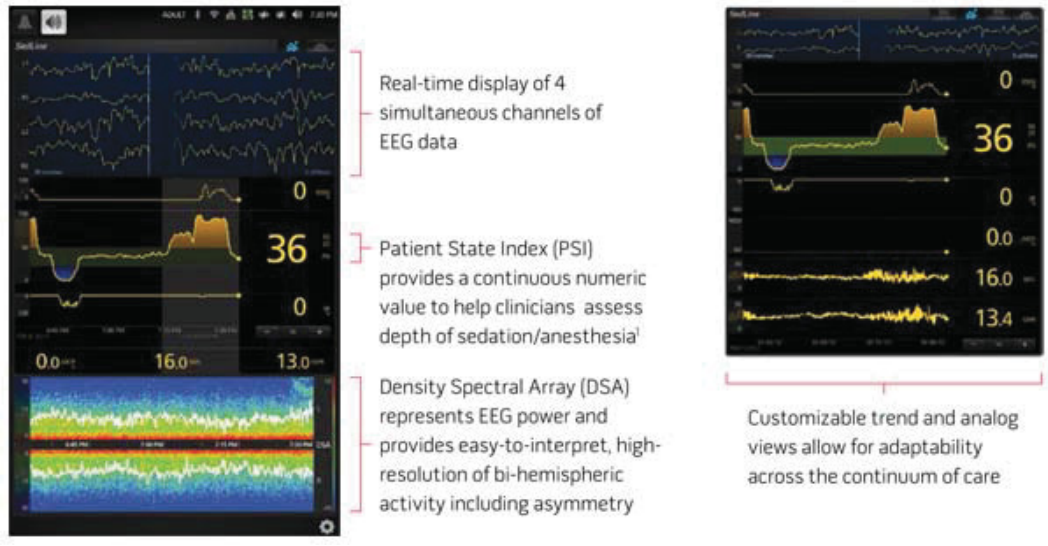

Figure 4: SedLine screen views.

The SedLine module easily plugs into the Root patient monitoring platform via Masimo Open Connect™ (MOC-9™) ports. (Figure 5)

Figure 5: SedLine connection into Root.

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. (Figure 6)

Figure 6: The SedLine EEG sensor array.

3. STUDY DESIGN

.3.1 Type of Study

This will be a prospective, single-center, open label pilot study undergoing sedation for sleep endoscopy. This will be a non-intervention data collection study as use of the research data will not be used to modify the patients' care.

Our objective is to improve guidelines for monitoring patients during sedation procedures while better understanding the anatomic changes of airway obstruction and the ability of respiratory acoustic monitoring to detect such obstruction.

Further, it is our goal to characterize the EEG signals when subjects are under dexmedetomidine sedation.

.3.2 Endpoints

Primary Endpoints:

- Endoscopic confirmation of airway obstruction
- RRa acoustic signal at moment of airway obstruction.
- EEG signal on SEDLine from patients under DEX sedation.

Secondary Endpoints:

- Peripheral oxygen saturation, SpO2

.3.3 Number of Subjects

This will be a pilot study with target of 60 subjects undergoing sedation for sleep endoscopy.

.3.4 Sample Size and Statistical Considerations

This is a pilot study of 60 subjects. An interim analysis is planned after the first 25 subjects. The goal of the interim analysis is to assess quality of the data and this interim analysis is not designed to terminate the study early. A power analysis is not feasible since there is no preliminary data. We will provide an Interim Analysis and Report at the end of the study.

.3.5 Patient stratification

Patients will be subdivided into the following 3 groups based on the type of anesthesia, the sedation period, the sleep endoscopy plan, and the anesthesiologist preferences:

1) patients requiring DEX sedation but non-requiring subsequent general anesthesia,

2) patients requiring DEX sedation and then proceed on to propofol induction of anesthesia, and

3) patients requiring DEX sedation and then proceed on to ketamine induction of anesthesia.

We will strive to obtain roughly equal numbers of patient enrollment in all 3 groups.

.3.6 Expected Duration of Study

We expect to enroll all patients in a 5 month period.

.3.7 Data Analysis Plan

There will be an interim analysis planned after the first 25 subjects, and a final analysis after completion of study enrollment. The goal of the interim analysis is to assess quality of the data and this interim analysis is not designed to terminate the study early.

Primary Analysis:

.3.7.1 Correlate sound pattern as recorded by the Masimo RRa (1) at moment of airway obstruction with endoscopic view of the airway obstruction. There will be simultaneous endoscopic video recording of the airway with digital recording of the RRa auditory signal.

.3.7.2 Correlate blood concentration of DEX with EEG on SEDLine (2) at baseline periods when DEX is first administered, as well as period later when DEX is being removed from patient's system and EEG is returning to normal

Secondary Endpoints:

.3.7.3 Correlate level of sedation (PSI) with obstruction.

.3.7.4 Correlate peripheral oxygen saturation with periods of airway obstruction observed via video recording during sleep endoscopy.

.3.7.5 Correlation of administration of anesthesia drugs (used as part of this routine care) with EEG response.

4. EQUIPMENT AND MATERIALS

- Commercially released Radical-7 and Root™ Rainbow Technology Multi-Function Docking Station (Masimo Corp) equipped with Acoustic Respiration Rate, SedLine, Oxygen Saturation, Pulse Rate, Perfusion Index.
- SedLine patient modules.
- Appropriate Masimo sensors (finger pulse oximetry sensors, neck respiratory sensors, forehead EEG sensors – all commercially released) and cables used with Radical-7 and Root devices.
- Equipment cart to hold the devices.
- Laptop computer with data collection software.
- Power strips and power cords.

5. SUBJECT ENROLLMENT

5.1 Recruitment

Potential subjects will be pre-screened and selected from a pool of patients undergoing sleep endoscopy procedure. The Principal Investigator and/or designated personal that is able to perform consent will obtain consent prior to actual procedure time. PI and/or designee will devote at least 30 minutes or more for the discussion of the consent.

The consenting process will be conducted in a private room. PI and/or designee will make it very clear to the subject that participation is entirely voluntary and will not affect subject's treatment. Study subject will be given the opportunity to ask questions throughout the consenting process. Subject will be given privacy and adequate time to consider the consent after initial discussion. Once the consent is signed by the subject and the PI or designee, a copy of the consent form will be given to the subject.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

- Adult patients more than 18 years old with ASA classification of I, II, or III.
- Patients undergoing sedation for sleep endoscopy with DEX alone, and possible surgical follow-up.

5.2.2 Exclusion Criteria

- ASA classification higher than III.
- Any deformities or diseases that may prevent application of SedLine or RAM sensors with a proper fit
- Inability to obtain any physiological, vital, demographics and real time anaesthesia data

- Subjects who have known intolerance to any of the drugs to be used according to the study protocol
- Subjects deemed not suitable for study at the discretion of the Principal Investigator.

5.3 Subject Withdrawal

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 recording the data.

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.

6. STUDY PROCEDURES

6.1 Patients will not receive pre-medication since this will disrupt the outcome of the sleep endoscopy operating room procedure.

6.2 Sensors will be placed onto the patient before being transferred to the sleep endoscopy operating room.

6.2.1 A SEDLine sensor array will be applied to the forehead of all patients to allow monitoring of adequacy of anesthesia using the patient state index (PSI). When applying the SedLine sensor array, manufacturer's directions for use should be followed, each lead will be checked to make sure good contact is established with all electrodes. Good contact is indicated by a green color on the electrode status display on Root.

6.2.2 A RAM (Rainbow Acoustic Monitoring) sensor will be placed on the subject's neck for acoustic respiratory monitoring.

6.2.3 Pulse oximetry sensors will be placed on subjects' fingers for standard pulse oximetry recording.

6.2.4 The sensors and cables will be connected to the Masimo Radical 7 or ROOT monitor with the following measurements: Acoustic respiration rate, SedLine EEG, oxygen saturation, pulse rate, perfusion index.

6.3 As part of standard of care, patients will receive standard monitoring consisting of SpO2, non-invasive blood measurement and ECG monitoring.

6.4 SedLine EEG and RAM RRa will be recorded for 3 minutes before administration of Dex to gather a clean baseline signal before administration of anesthetics.

6.5 Richmond Agitation-Sedation Score (RASS) score will be recorded at baseline (pre-DEX sedation). During DEX sedation, RASS score will be recorded every 5 minutes until the end of the Drug-Induced Sleep Endoscopy (DISE) procedure. For those patients who will not continue on to a general anesthesia, RASS score will be recorded every 15 minutes until the end of DEX sampling. For those patients who will be going on to general anesthesia, Observer's Assessment of Alertness/Sedation (OAAS) will be recorded post propofol or ketamine induction.

6.6 Patients will breathe room air during the DEX sedation component of the procedure. Sedation will be accomplished by DEX infusion by standard practice of the attending

anesthesiologist to accomplish sleep. Patients can receive ondansetron prn for episodes of nausea although this is a very uncommon event. Patients may receive intravenous glycopyrrolate if they have excessive secretions.

6.7 Patients will be supine. The patients' nose will receive lidocaine applied topically to provide comfort for the endoscopy component of the procedure.

6.1 Drug Dosing:

6.2 Anesthesia Steps:

6.3 Blood Samples:

6.3.1 To facilitate correlation of DEX with both EEG response and airway obstruction, samples of blood may be obtained for later analysis of DEX concentrations. To avoid contamination of blood samples with infused drug and avoid further needle puncture for samples, a second intravenous may be placed to obtain blood samples. Samples for DEX may be taken every 15 minutes after start of DEX infusion until 2 hours after DEX infusion is complete. There may be a maximum of 8 blood samples of volume of 1 ml. (See Appendix A for Handling Instructions)

7. MEASUREMENTS

Pre-operative

- Demographics, pre-anesthesia evaluation for medication history, and other pre-operative data will be recorded for all patients
- Other pre-operative assessment will include the following measures:
- 1) Apnea Hypopnea Index (AHI),
- 2) Hypopnea Index (HI),
- 3) Oxygen Desaturation Index (ODI),
- 4) Respiratory Disturbance Index (RDI),
- 5) Obstructive Apnea Index (OAI),
- 6) Minimum and mean oxygen saturation, and
- 7) RASS score.

Intraoperative

- Masimo Acoustic Respiration Rate
- Masimo Peripheral Oxygen Saturation
- Pulse rate
- Blood pressure
- Heart rate
- SEDLine PSI values
- SEDLine raw EEG
- RASS scores during DEX sedation
- OAA/S post propofol or ketamine induction
- Respiratory rate
- Dose and all infusion rates of DEX, ketamine and propofol
- Duration of anesthesia
- Duration of surgery
- Time to eye opening after sedation
- Time to following command after sedation

Post-operative

- Any adverse events

8. DOCUMENTATION AND DATA MANAGEMENT

8.1 Screening and Enrollment Logs

A subject screening and enrollment log will be created and will record all eligible and non-eligible subjects, documenting informed consent, as well as refused consent and other reasons if subject was excluded or withdrawn.

8.2 Device accountability

Site will maintain a device accountability log identifying devices received, used and returned. A log template will be provided to site by sponsor for this purpose.

8.3 Protocol deviations

Protocol deviations are accidental or unintentional changes to, or non-compliance with, the research protocol that does not increase the risk, decrease the benefit or have a significant effect on the subject's rights, safety or welfare.

All Protocol Deviations must be recorded in the Protocol Deviations Form, within the CRF.

In the event that Protocol Deviations occur, the Protocol Deviation Reports must be signed and dated by the Principal Investigator.

All Protocol Deviations must be reported to the Sponsor and to the IRB.

8.4 Device deficiencies

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

All Device Deficiencies, including but not limited to malfunctions or unexpected behaviors, must be recorded in the Device Deficiencies Form, within the CRF.

In the event that Device Deficiencies occur, the Device Deficiency Reports must be signed and dated by the Principal Investigator.

All Device Deficiencies must be promptly reported to the Sponsor.

8.5 Case report form (CRF)

The Sponsor shall provide a paper 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 completed and signed by principal investigator. 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, RR manual measurements, patient feedback such as discomfort or ability to tolerate sensor application, patient skin condition after sensor removal, name of ADC file, name of data collector, and if occurrence of any adverse event, protocol deviation, and device deficiencies, etc.

The CRF will be signed by the PI and forwarded to Masimo.

CRF entries will be checked by study monitor 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.

8.6 Data collection

Data will be collected continuously from the ADC during the pre-, intra- and post-operative period. Other data including age, past or current illness, weight, gender, etc. will be collected on case record forms (CRF).

Blood samples will be shipped to the iC42 Clinical Research and Development Laboratory and will be analyzed for concentration of Dexmedetomidine using a qualified/validated LC-MS/MS method at the laboratory. Results of the DEX blood concentration analysis will be sent back to the study site electronically.

8.7 Data Transfer and Storage

The information will be stored in a password protected electronic database at the study site. Device data along with an electronic copy of the CRF will periodically be securely uploaded to sponsor via secure FTP portal.

Only authorized sponsor personnel will have access to the transferred data, and will move it to a secure and backed-up drive at Masimo.

Device data and electronic copy 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 correction. If the investigator/staff is to correct the CRF, the PI/staff shall follow GDP practices to strike thru old entry, add in new entry, and initial and date it, and resend to Masimo the corrected CRF. [redacted] Raw and processed physiological data will be analyzed by Masimo Engineering team.

8.8 Site Study 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.

9. MONITORING PLAN

9.1 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.

9.2 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 every year, or within 3 months of a significant data collection round
- A final close out visit after the last patient had finished the study.

9.3 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.

9.4 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.

9.5 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.

9.6 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 16 for details on suspension and termination.

9.7 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.

10. PATIENT AND DATA SAFETY MONITORING AND REPORTING

10.1 No monitoring by a data and safety monitoring board is planned, since this is an observational study, with no treatment decisions based on the study.

11. RISK ANALYSIS

11.1 This is an observational study using FDA cleared noninvasive devices with no planned interventions outside of the standard of care.

11.2 The medical devices in use, the Masimo Radical-7, ROOT, SedLine, RAM devices with their corresponding sensors, are non-significant risk (NSR) devices and make non-invasive recordings. All devices and sensors to be used for this study are currently cleared by the FDA to be used in the Adult and Pediatric population. Masimo devices and sensors have been used in a wide range of hospital and clinical settings, and have been studied and validated in many independent studies, and shown to be safe and effective for monitoring use.

11.3 Potential Risks to Participants & Anticipated Adverse events

11.3.1 There is a rare possibility that subjects could experience an allergic reaction to the adhesive in the sensor. The clinical investigators do not anticipate any additional risks to the subjects as a result of the devices and sensors used in this study.

11.3.2 Venous Blood Draw: The most common complications associated with venous draws are hematoma and bruising.

11.3.3 As with all optical sensors, the pulse CO-oximetry sensors used in this study has the risk of thermal burn. The design includes safeguards, and this risk is believed to be low. These sensors use wavelengths in the red and near infrared range like a conventional pulse oximeter used in routine clinical practice for over 15 years.

12. ADVERSE EVENT

12.1 Definitions:

a) 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)).
b) Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
c) 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.
d) 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.
e) 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.
f) 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.

12.2 Anticipated Adverse Event:

All devices and sensors to be used for this study are Non-Significant Risk; however, there is still the possibility for the following Anticipated Adverse Events to occur:

- Allergic reactions to sensor adhesives.
- Allergic reactions to SedLine sensor gel.
- Allergic reactions to any other sensor materials that may contact skin.
- Skin discomfort, irritation, redness from applying or removing sensor adhesives.
- Bruising from venous blood draw
- Airway obstruction,
- Side effects of endoscopy procedure: hypertension, bradycardia, nausea.

12.3 Adverse Event Reporting:

a) All Adverse Events, both Anticipated and Unanticipated, must be recorded in the Adverse Event Report Form, within the CRF.
b) In the event that an Adverse Event occurs, the Adverse Event must be assessed by the Principal Investigator, and the Adverse Event Report must be signed and dated by the Principal Investigator.
c) If more than one Adverse Events occur for the same subject, each Adverse Event will be reported separately on a copy of the Adverse Event Report Form.
d) All Adverse Events must be promptly reported to the Sponsor.
e) All Unanticipated Adverse Device Effects will be also reported to both the Sponsor and the IRB.
f) 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.
g) 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.

13. MEASURES TAKEN TO PROTECT THE RIGHTS AND WELFARE OF THE SUBJECTS

13.1 The study will be performed according to the Declaration of Helsinki principles, and written informed consent will be obtained from each subject prior to any study procedures being conducted. Subjects will be provided with oral and written information about the study. Subjects will be given adequate time and privacy to consider their consent.

13.2 All subjects will be monitored closely by study staff throughout the study.

13.3 The following measures will be taken to ensure the privacy of the subjects.

13.3.1 Subjects will only be identified in the study by a unique Subject ID number.

13.3.2 Protected Health Information (PHI) for study Subjects will be stored and locked away at the investigator's research site only.

13.3.3 Sponsor may have access to PHI at times, only temporarily during auditing/monitoring functions.

13.3.4 The confidentiality of these documents will be protected to the extent provided by the law.

14. POTENTIAL BENEFITS TO PARTICIPANTS

The study team does not anticipate any individual benefits to study participants. The goal of this study is to gain information that may help make anesthesia safer for future anesthesia patients.

15. COMPENSATION TO PARTICIPANTS

No monetary compensation will be provided to study participants.

16. ADMINISTRATIVE ASPECTS

16.1 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.

16.2 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 redline version and a clean version of the new protocol amendment will be kept on file by the PI and the sponsor. 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.

16.3 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.

16.4 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 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.

17. AGREEMENT BETWEEN INVESTIGATOR AND SPONSOR REGARDING RESPONSIBILITIES FOR GOOD CLINICAL PRACTICE

17.1 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.

17.2 It specifies general requirements intended to:

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

17.3 The Principal Investigator of the clinical investigation shall:

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

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

APPENDIX A

Pharmacokinetic Sample Handling _Dexmedetomidine_plasma_150722.pdf

REFERENCES

1. Ramsay MA, Usman M, Lagow E, Mendoza M, Untalan E, De Vol E. The accuracy, precision and reliability of measuring ventilatory rate and detecting ventilatory pause by rainbow acoustic monitoring and capnometry. Anesth Analg. 2013 Jul;117(1):69-75
2. Drover D. Patient state index. Best Pract Research Clin Anaesthesiol 2006;20:121-128.

3. 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.
4. John, E.R., A field theory of consciousness. Conscious Cogn., 2001. 10(2): p. 184-213.
5. 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.
6. Pittman SD, Ayas NT, MacDonald MM, Malhotra A, Fogel RB, White DP. Using a wrist-worn device based on peripheral arterial tonometry to diagnose obstructive sleep apnea: in-laboratory and ambulatory validation. Sleep. 2004 Aug 1;27(5):923-33.
7. Jordan AS, White DP, Lo YL, Wellman A, Eckert DJ, Yim-Yeh S, Eikermann M, Smith SA, Stevenson KE, Malhotra A. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep. 2009 Mar;32(3):361-8.
8. Fogel RB, Trinder J, White DP, Malhotra A, Raneri J, Schory K, Kleverlaan D, Pierce RJ. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. J Physiol. 2005 Apr 15;564(Pt 2):549-62.Zheng Chen, Dong-Hua Shao, Li-Hua Hang.
9. Zheng Chen, Dong-Hua Shao, Li-Hua Hang Effects of dexmedetomidine on performance of bispectral index as an indicator of loss of consciousness during propofol administration, Swiss Med Wkly. 2013;143: w13762
10. K. Kaskinoro, A. Maksimow, J. Långsjö, R. Aantaa, S. Jääskeläinen, K. Kaisti, M. Särkelä, and H. Scheinin. Wide inter-individual variability of bispectral index and spectral entropy at loss of consciousness during increasing concentrations of dexmedetomidine, propofol, .and sevoflurane. British Journal of Anaesthesia 6 July, 2011

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