Official Title: Oxygen Reserve Index: Utility as Early Warning for Desaturation in Morbidly Obese Patients

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Oxygen Reserve Index: Utility as Early Warning for Desaturation in Morbidly Obese Patients

Sponsor: Masimo
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Principal Investigator: Neal W. Fleming, MD, PhD

Study Devices:
Masimo Radical 7 Rainbow monitoring device
Masimo Root Patient Monitoring and Connectivity Platform
[redacted]
Masimo Rainbow Disposable optical sensors
Masimo Rainbow RC-4 20 pin patient cable (PN 2406)
[redacted]
[redacted]
Investigational devices and sensors of a similar use and design as FDA-cleared devices and sensors

Sponsor Protocol Number: FLEM0004

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1 INTRODUCTION

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

1.1 Background and Rationale

Obese patients are presenting with increasing frequency for elective and emergent surgical procedures. Obesity is associated with an increased incidence of perioperative morbidities, including pulmonary complications. Airway management in these patients presents potential problems associated with both the physical and physiological changes of obesity. Pre-oxygenation is more difficult and unpredictable (Shah, et al.), maintenance of a patent airway can be more difficult (Langeron et al.) and obese patients desaturate more rapidly during periods of apnea (Jense, et al.). As a consequence, arterial oxygen desaturation is more common and more severe in this patient population (Bodily et al.).

The measurement of arterial hemoglobin saturation by comparing the absorbance of infrared light in arterial and venous blood has revolutionized anesthetic practice, providing a standard monitor that has increased patient safety in nearly every clinical setting. Expansion of this technology to include the measurement of additional wavelengths (up to 8 or more) led to the development of continuous hemoglobin monitoring. We have evaluated this hemoglobin monitoring system extensively under a related IRB protocol [redacted]

Additional information that is obtainable from the expanded number of wavelengths has also been shown to correlate with pA_{O2} values in the moderately hyperoxic region (Applegate et al.). This information can be characterized as the Oxygen Reserve Index (ORI). [redacted] This index is designed to supplement standard arterial hemoglobin saturation monitoring. (ORI Whitepaper) Preliminary studies have evaluated the relationship between ORI and pA_{O2} in the general surgical population (Applegate et al.). In addition, the ORI has been demonstrated to provide a clinically useful advanced warning of impending arterial hemoglobin desaturation in pediatric patients. (Szmuk et al.) The relationship between ORI and standard saturation monitoring is characterized by this illustration from the above referenced whitepaper:

This protocol is designed to evaluate the potential utility of ORI to serve as an early warning of impending arterial hemoglobin desaturation during the induction of general anesthesia and endotracheal intubation in obese patients.

References:

Shah U, Wong J, Wong DT, Chung F. Pre-oxygenation and intraoperative ventilation strategies in obese patients: a comprehensive review. Curr Opin Anesthesiol 29:109–118, 2016

Langeron O, Birenbaum A, Le Sache F, Raux M. Airway management in obese patient Minerva Anestesiol 80:382-92, 2014

Jense HG, Dubin SA, Silverstein PI, O'Leary-Escolas U. Effect of Obesity on Safe Duration of Apnea in Anesthetized Humans. Anesth & Analg;72:89-93, 1991

Bodily JB, Webb HR, Weiss SJ, Braude DA. Incidence and Duration of Continuously Measured Oxygen Desaturation During Emergency Department Intubation. Ann Emerg Med;67:389-395, 2016

Applegate RL, Dorotta IL, Wells B, Juma D, Applegate PM. Relationship Between Oxygen Reserve Index and Arterial partial Pressure of Oxygen During Surgery. Anesthesia & Analgesia, e-published ahead of print March 22, 2016

Oxygen Reserve Index (ORITM). Available at: http://www.masimo.co.uk/pdf/ori/LAB8543A_Whitepaper_ORI_British.pdf Accessed March 11, 2016

Szmuk P, Steiner JW, Olomu PN, Ploski RP, Sessler DI, Ezri T. Oxygen Reserve Index: A novel Noninvasive Measure of Oxygen Reserve – A Pilot Study. Anesthesiology;124:779-84, 2016

1.2 Study Device

The Masimo Radical-7 is a noninvasive monitor that measures arterial oxygen saturation (SpO2), pulse rate (PR), and perfusion index (PI), along with optional measurements of hemoglobin (SpHb), carboxyhemoglobin (SpCO®), total oxygen content (SpOC), methemoglobin (SpMet), Pleth Variability Index (PVI®), Oxygen Reserve Index (ORI™), Acoustic Respiration Rate (RRa®), and Pleth Respiration Rate (RRp). Masimo SET® technology is clinically proven to satisfy all sensitivity and specificity requirements for pulse oximetry. Masimo rainbow® technology uses 7+ wavelengths of light to continuously and noninvasively measure carboxyhemoglobin (SpCO), methemoglobin (SpMet), and total hemoglobin (SpHb®), as well as providing a more reliable probe-off detection. Total oxygen content (SpOC) provides a calculated measurement of the amount of oxygen in arterial blood, which may provide useful information about oxygen both dissolved in plasma and combined with hemoglobin. Perfusion Index (PI) with trending capability indicates arterial pulse signal strength and may be used as a diagnostic tool during low perfusion. Pleth Variability Index (PVI) may show changes that reflect physiologic factors such as vascular tone, circulating blood volume, and intrathoracic pressure excursions. [The utility of PVI is unknown at this time and requires further clinical studies. Technical factors that may affect PVI include probe

malposition and patient motion.] Oxygen Reserve Index (ORI) is an index measured noninvasively and continuously to provide an earlier indication of impending hypoxia by extending oxygen monitoring of pulse-oximetry to the moderate hyperoxic regions. Respiration rate can be determined by the acoustic (RRa) or plethysmographic waveform (RRp). Signal IQ is a feature for signal identification and quality indication during excessive motion and low signal to noise situations. FastSat® tracks rapid changes in arterial O2. A detailed description of the Masimo Radical-7 can be found in the attached manual.

1.3 Risk/Benefits

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

Sensor risks: As with all optical sensors, the investigational device has the risk of thermal burn. Pulse CO-oximeter noninvasive measurement uses wavelengths in the red and near infrared range like a conventional pulse oximeter used in routine clinical practice for over 15 years. The additional LEDs from Rainbow sensors have been tested and meet the Exempt classification for photo-biological safety of light sources.

All patient-contact materials, including the adhesive used in the design of the Masimo Rainbow 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.

No other physical, financial, social or psychological risks are anticipated to be associated with participation in this study as it only observation with the recording of intraoperative ORI and ABG measurements. Precautions taken to safeguard protected personal health information are described in the section on recruitment. The risks associated with the anesthetic and surgical procedure are not discussed in this proposal

2 STUDY OBJECTIVES

This is a prospective, observational study of the Oxygen Reserve Index (ORI) in a clinical setting designed to evaluate its clinical utility as an early warning for arterial oxygen desaturation in a specific patient population.

Specific aims:

- evaluate the clinical utility of the change in the oxygen reserve index as an early warning of impending arterial oxygen desaturation in obese patients

- characterize the impact of the oxygen reserve index on the incidence of arterial hemoglobin desaturation during the induction of general anesthesia and tracheal intubation in obese patients

Hypothesis (constructed as the null):

Intraoperative changes in the oxygen reserve index will not provide additional clinically significant data with respect to the efficacy of pre-oxygenation or warning for arterial desaturation and will not decrease the incidence of arterial hemoglobin desaturation during induction of general anesthesia and tracheal intubation in obese patients.

3 STUDY DESIGN

This is a prospective, observational, clinical study designed to evaluate the clinical utility of the ORI as an early warning for arterial hemoglobin desaturation during the induction of general anesthesia and tracheal intubation in obese patients undergoing elective surgical procedures. In addition, data will collected from non-obese patients to serve as a control group population.

3.1 Study Endpoints

Primary study endpoints include a characterization of the utility of the oxygen reserve index as a guide for pre-oxygenation and an earlier warning for arterial oxygen desaturation to decrease the incidence of arterial hemoglobin desaturation during the induction of general anesthesia and tracheal intubation in obese patients.

4 CLINICAL TEST SITE

UC Davis Medical Center, Main Hospital, Pavilion operating rooms

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

Patients scheduled for elective surgical procedures in the UC Davis Medical Center main ORs will be screened for potential enrollment. Up to 80 patients will be enrolled.

5.2 Inclusion Criteria

- Age greater than 18 years
- BMI>30, <40 m/kg^2
- Control group only: BMI >18.5 m/kg^2, <25 m/kg^2
- Scheduled for an elective surgical procedure requiring general anesthesia and endotracheal intubation

Exclusion Criteria

- Age less than 18 years
- Adults unable to give primary consent
- Pregnancy
- Prisoners

5.3 Study Timelines

- Each individual patient will participate only for the duration of their anesthetic induction which may vary from 5 to 15 minutes.

- This study is anticipated to require up to 3 months for completion of patient enrollment.

- Primary analysis of the data is expected to require an additional 6 months.

5.4 Subject Recruitment and Screening

Patient recruitment and informed consent will be obtained in the 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.

HIPAA

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.

5.5 Withdrawal of Subjects

Informed consent discussions will explicitly include emphasis that neither patient enrollment nor patient withdrawal from the study will result in any alterations to the standard clinical care. Subjects may elect to withdraw at any time up to the induction of general anesthesia. Because this is an observational trial, unforeseen changes in the clinical care plan (change in surgical procedure, emergent management changes) simply trigger a discontinuation of the additional monitoring.

6 STUDY DEVICE

Investigational Devices:

Masimo investigational pulse CO-oximeter devices and/or sensors, with the same or similar technology and materials as the Masimo FDA cleared devices and sensors, that pose no additional risk to human subjects than the FDA cleared devices and sensors.

[redacted]

FDA-cleared Devices:

Masimo Radical 7 Rainbow monitoring device
Masimo Root Patient Monitoring and Connectivity Platform
[redacted]
Masimo Rainbow Disposable optical sensors
Masimo Rainbow RC-4 20 pin patient cable (PN 2406)
[redacted]
Investigational devices and sensors of a similar use and design as FDA- cleared devices and sensors

6.1 Device Accountability

6.1.1 Receipt of Study Device

Upon receipt of the of the study device supplies, an inventory must be performed and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

6.1.2 Use of Study Device

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

6.1.3 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.

7 STUDY PROCEDURES

- Following arrival of the patient in the operating room all standard and planned physiological monitors will be placed. A baseline ORI will be measured.

- As per routine, all patients will be pre-oxygenated with 100% oxygen.

- All patients will be managed with the additional information from the ORI monitor. During pre-oxygenation, [redacted] general anesthesia will be induced with a combination of amnestics, narcotics, intravenous induction agents and

muscle relaxants as clinically indicated. Endotracheal intubation will be under direct visualization using a GlideScope. When the arterial hemoglobin saturation [redacted] ventilation will be initiated with [redacted] either via the endotracheal tube or resumed mask ventilation. The changes in ORI and arterial hemoglobin saturation will be recorded continuously [redacted]

8 STATISTICAL PLAN

Sample size estimate: The planned sample size for this protocol is determined by the first specific aim: to evaluate the clinical utility of the change in the oxygen reserve index as an early warning of impending desaturation in the critically ill patient. A total of 80 patients are planned, 40 in the normal BMI range and 40 in the morbidly obese BMI range. To determine the appropriate sample size we extrapolated from Szmuk et al. and their measurement of the times for arterial hemoglobin saturation to decrease from 98% to 90%. Next, we then postulated that a clinically significant improvement would be 30 seconds of advanced warning. Based upon the reported mean and standard deviation, with a power of 0.8, the estimated required sample size was 34 patients in each study group. This estimate was then increased to 40 to account for incomplete data collection and potential dropouts. Because of the limited data available to establish the variance of this measurement we plan an interim analysis after 20 patients.

9 SAFETY AND ADVERSE EVENTS

9.1 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.

9.2 Anticipated Adverse Events:

Mild allergic reaction to sensor material and adhesives.
Discomfort, redness or skin irritation.

9.3 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.

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

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

Protocol Deviations
Any protocol deviations initiated without Sponsor and/or 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.

10 DATA MANAGEMENT

10.1 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 in the UCDMC perioperative suite only 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 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.

10.2 Data Management and Confidentiality

All documents associated with this protocol will be kept in the locked office of the PI 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 protocol. 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. Data will be retained for up to 2 years following completion of the final analysis.

10.3 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.

10.4 Case Report Forms

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, device readings, 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. The monitor or study manager will collect original completed and signed CRFs at the end of the case. A copy of the completed and signed CRFs will remain on site.

10.5 Data Transfer and Storage

10.5.1 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.

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

10.5.3 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 is to correct the CRF, the PI 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. 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 data, therefore are unable to unintentionally tamper with the original data files. Raw and processed physiological data will be analyzed by Masimo Engineering team.

10.6 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.

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/or every year
- 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 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.

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 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.

12.2 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.

12.3 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.

12.4 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.

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.