Official Title: Performance Comparison of Masimo O3 Regional Oximetry Device in Neonates

Date of Protocol: 14 February 2019

NCT Number: NCT03828487

Performance Comparison of Masimo O3 Regional Oximetry Device in Neonates

Sponsor: Masimo
52 Discovery
Irvine, CA 92618

Primary Investigator: Dr. Chandra Ramamoorthy

Study Devices:

Masimo Radical-7 monitoring devices

Masimo Root® Patient Monitoring and Connectivity Platform

Masimo O3 Regional Oximetry System

Masimo O3 Neonatal Sensor

Masimo RD SET Pulse Oximetry Sensors

[redacted]

Sponsor Protocol Number: RAMA0004

IRB: Stanford University Medical Center
300 Pasteur Dr.
Stanford, CA 94305

Principal Investigator	Title	Signature	Date
Chandra Ramamoorthy. MD	Principal Investigator		
Sponsor	**Title**	**Signature**	**Date**
Vikram Ramakanth	Director, Clinical Research		

1 INTRODUCTION

This document is a protocol for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki. In participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of IRB/IEC approval, ISO-14155, and International Conference on Harmonization Good Clinical Practice guidelines ICH GCP.

1.1 Background and Rationale

Masimo Corporation is a developer of noninvasive technologies for the measurement and monitoring of physiological variables, such as arterial oxygen saturation (SpO_2), total hemoglobin concentration (SpHb), carboxyhemoglobin concentration (SpCO), methemoglobin concentration (SpMet) and acoustic respiration rate monitoring (RRa). These technologies are noninvasive and have a good patient safety record.

Masimo has also developed regional oximetry technology for the detection of deep tissue oxygen saturation. The Masimo O3™ monitoring system consists of a bedside monitor, the O3 regional oximeter module, and near infra-red spectroscopy (NIRS) sensors. NIRS has become an essential tool for monitoring cerebral oxygenation during sedation, operation especially in pediatric patients. Additionally, using NIRS to monitor the difference between somatic and cerebral oxygenation may provide additional physiological information. Published studies (Hoffman et al) have shown that this non-invasive methodology is useful for early and quantitative detection of shock. It has also been shown to be related to the adequacy of mean arterial pressure (MAP), hematocrit, and PaCO2 during cardiopulmonary bypass (White *et al.*).

The Masimo O3 Regional Oximeter consists of the following components as a system: O3 Module, O3 Sensor, and Masimo Root (display monitor). The O3 Module receives power from the display monitor. The measurements are generated from the O3 Sensor attached to the patient at proximal end and connected to the O3 Module at the distal end. The measures are taken and displayed on the Masimo Root monitor. The O3 regional oximeter sensors contain a 4-wavelength LED emitter and two light detectors for the detection of deep tissue and superficial oxygenation. The system is designed to allow the near-infrared light to superficially penetrate the scalp, skull and brain tissue. Using multiple wavelengths of light and spatially distributed photo-detectors to interrogate the deep tissue, the O3 system measures regional saturation of oxygen (rSO_2) by establishing a relationship between the light absorbed by the tissue and its oxygen saturation. The O3 system has received US FDA 510(k) clearance for adult and pediatric patients.

In addition to the 510(k) cleared adult and pediatric O3 sensors, Masimo has also developed an O3 neonatal sensor for use with the neonatal population. This investigational sensor is similar to the FDA-cleared adult and pediatric sensors in design and intended use, however the sensor footprint has been reduced for these patients. [redacted]

1.2 Study Devices

Investigational

- Masimo O3 Neonatal sensors

Cleared Devices

- Masimo O3 Regional Oximetry System
- Masimo Radical-7 pulse co-oximeter device
- Masimo RD SET Pulse Oximeters
- Masimo Root patient monitoring and connectivity platform

[redacted]

1.3 Risk/Benefits

Benefits: There is no benefit to the individual for participation in this research study. No compensation will be paid to the participants or their families. Future benefits might include a reduction in invasive procedures due to the ability to obtain noninvasive blood parameter measurements.

Risks: Risks from all Masimo sensors are minimal since the technology uses non-invasive optical sensors.

As with all optical sensors, the investigational device has the risk of thermal burn. The design includes safeguards and this risk is believed to be low. Pressure damage may occur to the tissue if the sensor is placed too tightly. Sensors will be attached with adhesive and may be secured by a supplemental headband. This risk is believed to be low. Optical exposure is minimized by procedure and low power.

All patient-contacting materials including the adhesive used in the design of the regional oximetry sensors are biocompatible, compliant with ISO-10993-5 and ISO-10993-10 testing, and the results demonstrate that the materials are non-toxic, and non-irritating, and non-sensitization. The sensors have been subjected to performance, mechanical, and electrical testing, skin surface temperature and results demonstrate that the sensors meet the requirements for safety and effectiveness for intended use of the product, refer to investigational brochure for further details.

Patient cable risk: Entanglement of the sensor cables may occur but the research personnel will be present during the study to avoid such an occurrence.

2 STUDY OBJECTIVES

The aim of the study is to compare the performance of the O3 cerebral oximeter and sensor to a 510(k) cleared NIRS device on neonatal subjects based on data collected from the cutaneously placed forehead sensors. [redacted]

3 STUDY DESIGN

This is a prospective, non-randomized, single arm study design to compare the cerebral oxygenation trending data between Masimo's neonatal sensor and a currently cleared NIRS device in the neonatal population using convenience sampling in a clinical environment. This study may be used to support regulatory filings for Masimo O3 system using the neonatal sensor.

4 CLINICAL TEST SITE(S)

Stanford University Medical Center
300 Pasteur Dr.
Stanford, CA 94305

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

Subjects will be healthy and non-healthy newborns at Stanford University Medical Center. A convenience sampling with at least 10 subjects and up to 25 subjects with diversified demographics (age, gender, ethnicity, skin tone, comorbidities, etc.) will be recruited and enrolled at this site with the following inclusion and exclusion criteria.

5.2 Inclusion Criteria

- Less than 10 kg
- Subjects less than or equal to 28 days old

5.3 Exclusion Criteria

- Underdeveloped skin at sites of sensor placement
- Jaundice or hyperbilirubin
- Subject has skin abnormalities affecting the sensor placement area such as psoriasis, eczema, angioma, scar tissue, burn, fungal infection, or substantial skin breakdown that would prevent monitoring of oxygenation levels during the study
- Subject deemed not eligible based on Principal Investigator's judgment

5.4 Study Timelines

The anticipated duration of subject participation in this study will not exceed 1 hour during their stay. The sensors may be placed continuously to enable noninvasive data collection. The study enrollment period is expected to be approximately 1 year.

5.5 Subject Recruitment and Screening

Potential subjects will be recruited from the patient pool at Stanford University Medical Center. A process for explaining the subject recruitment and screening for the clinical research study will take place during recruitment to determine if an individual is eligible to participate in the study. This will also include a description of the process for obtaining informed consent and HIPAA.

5.6 Withdrawal of Subjects

Informed consent discussions will explicitly include emphasis that neither patient enrollment nor patient withdrawal from the study will result in any alterations to the standard clinical care. Participant's parent/legal guardian may elect to withdraw their child at any time without any consequences or loss of benefits to which they are entitled. As the subject, the neonate may be withdrawn from the study prior to expected completion for reasons such as safety concerns, failure to protocol requirements, subject consent withdrawal, etc.

Any data collection until the time of subject's withdrawal may be included in the final data analysis unless the subject withdraws their consent. Information of the subject's withdrawal should be documented in the case report forms (CRFs) and include clear documentation of the reason for withdrawal to the Sponsor.

In case a subject leaves the study prematurely, another subject may be recruited.

6 STUDY DEVICE

6.1 Description

FDA-cleared device:

Masimo O3 regional oximetry uses near-infrared spectroscopy (NIRS) to continuously monitor absolute and trended regional tissue oxygen saturation (rSO2) in the cerebral region. It has received 510(k) clearance marking for use with adult and pediatric patients. The O3 system is comprised of a module, a sensor and a Root monitor. The Radical-7 pulse co-oximeter will be connected to Root patient monitoring platform. All components of the O3 system is cleared except for the sensor. The O3 Neonatal sensor will be considered as an investigational device.

The Root with Radical 7 Pulse CO-Oximeter and accessories are indicated for the continuous non-invasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO2), pulse rate, carboxyhemoglobin saturation (SpCO), methemoglobin saturation (SpMet), total hemoglobin concentration (SpHb), and/or respiratory rate (RRa). The Root is part of the O3 system as it is used to display the readings produced from the sensor.

The Radical 7 pulse CO-oximeter is a noninvasive patient monitor that continuously measures and monitors in real-time the oxygen saturation of arterial hemoglobin (SpO2), and pulse rate (PR), among other parameters, and is for use with adult, pediatric, and neonatal patients during both in motion and no motion conditions, and for patients who are well or poorly perfused in hospitals, hospital-type facilities, mobile, and home environments.

The RD SET™ Series disposable sensors are indicated for the continuous noninvasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO2) and pulse rate (measured by an SpO2 sensor) for use with adult, pediatric, infant, and neonatal patients during both no motion and motion conditions, and for patients who are well or poorly perfused in hospitals, hospital-type facilities, mobile, and home environments.

Investigational devices:

The investigational O3 Neonatal sensor is similar to the 510(k) cleared O3 Adult and Pediatric sensor in design and functionality. The neonatal sensor's physical design has been modified in dimension and shape to accommodate a better fit in neonatal patients. The neonatal sensor will be equipped with the same or similar technology and materials as the Masimo 510(k) cleared adult and pediatric sensors, and is not anticipated to pose additional risk to human subjects than the 510(k) cleared sensors.

6.2 Device Accountability

6.2.1 Receipt of Study Device

Upon receipt 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.

6.2.2 Use of Study Device

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

6.2.3 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.

6.2.4 Device Deficiencies

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

7 STUDY PROCEDURES

7.1 Informed Consent and Screening Procedure

7.1.1 Following identification of a potential eligible subject as defined by the inclusion and exclusion criteria, the child's parent(s), guardians(s), legally authorized representative, will be approached by the study staff. The study research staff will explain the purpose and procedures of the study in respect to potential risks & benefits, and clarification of subject's rights & privacy and allow ample amount of time for participating in the described study. The research team will emphasize that participation is voluntary, has no monetary compensation, and declining the participation will not affect their child's medical care.

7.1.2 As a subject, the neonate must meet all the inclusion criteria and none of the exclusion criteria prior to being enrolled in the study.

7.1.3 This protocol requires written informed consent in accordance with applicable federal and state regulations, as well institutional review board (IRB). If the child's parent(s)/legal guardian(s) express interest in participating in the study, they will be asked to read the written informed consent.

7.1.4 Once the parent(s)/legal guardian(s) questions have been answered and the informed consent signed and dated, the

Principal Investigator or delegate will also sign the informed consent document, approving that the subject will be enrolled in the study. The Investigator shall retain the original copy of the signed informed consent document in each subject's records and provide a copy to the subject. The investigator shall not enroll any subject to participate in the study or consent any subject prior to receiving IRB approval of the informed consent form.

7.1.5 Subject's demographic information which may include, but is not limited to: gender, age, weight, height, race, ethnicity, [redacted] will be recorded on the case report form (CRF).

7.2 **Noninvasive Readings**

7.2.1 Demographic information and medical history will be obtained for each enrolled subject prior to the start of the procedure.

7.2.2 One Masimo O3™ cerebral oximetry sensor and one 510(k) cleared sensor will be placed [redacted]

7.2.3 If there is no standard-of-care pulse oximetry sensor attached to the subject, a Masimo pulse oximetry sensor will be placed on to the subject. (If there is a standard of care sensor present, record the SpO2 reading from the standard-of-care sensor on the CRF prior to beginning data collection with any regional oximetry sensor. The Masimo sensor will not be used to make any clinical decisions and is only meant for data collection purposes.)

7.2.4 [redacted] Masimo's regional oximeter module will be connected to Root for regional oximetry data collection.

7.2.5 Masimo regional oximetry sensor will be connected to the O3 module (POD). [redacted] Record the start time on the CRF and begin data collection [redacted]

7.2.6 Collect data for at least five minutes. [redacted]

7.2.7 [redacted].

7.2.8 [redacted]

8 STATISTICAL ANALYSIS

8.1 **Sample Size Determination**

This study will use a convenience sampling of at least 10 subjects, but up to 25 subjects may be enrolled to account for possible events such as subject withdrawal, device deficiencies, and/or incomplete cases.

8.2 **Data Analysis**

There are no acceptance criteria for this study. Bias, Precision and RMS values will be calculated and reported between the two test devices but there are no invasive reference for actual accuracy measurements. Performance metrics are not required as this is a convenience sample study.

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 caused 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.

9.2 Anticipated Adverse Events:

Sensor may cause slight and temporary redness, skin discomfort or irritation, which should fade away shortly after sensor removal.

Sensor may cause thermal burn; however, the design includes safeguards and this risk is believed to be minimal.

Sensor may cause an allergic reaction to the adhesive or other materials used in the sensors; however, all patient contacting materials have undergone biocompatibility testing and conforms to all relevant standards.

9.3 Adverse Event Reporting:

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

9.4 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 possible, but no later than 5 working days after the protocol deviation.

9.5 Withdrawal of IRB approval

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

10 DATA MANAGEMENT

10.1 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.

10.2 Source Documents

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

10.3 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.

10.4 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 log 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 through old entry, add in new entry, and initial and date it, and resend the updated corrected CRF copy to Masimo. 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.

10.5 **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:

[redacted]

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

12 VULNERABLE POPULATIONS

12.1 **Definition**

12.1.1 Vulnerable population are research participants, such as children, prisoners, pregnant women, handicapped, or mentally disable persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to

coercion and undue influence. This study will recruit children from either economically or educationally disadvantaged families.

The federal regulations that govern the protection of human subjects (21 CFR Part 50, Subpart D) require additional protection for the vulnerable population.

12.2 Protection of vulnerable subjects

- For children, the Investigator will ensure that parent/legal guardian does not unduly influence subjects to participate (21CFR Part 50). Parents/legal guardian of the participant will have ample time to ask questions and understand the information being presented.
- Participant's parents/legal guardian with limited English skills will be provided translated documents in native language, staff/independent interpreter, and have ample time to ask questions and understand information.
- There is no undue influence to the parent/legal guardian of the participant due to no financial incentive for the economically disadvantaged subjects since there is no compensation for the completion or participation in this study.
- Educationally disadvantaged parent/legal guardian of the participant will be provided ample time to ask questions and comprehend the information.
- Medical care will be provided to these subjects after the clinical investigation has been completed if they are injured as a direct result of participating in this research study. The cost of treatment for any research related injury will be covered by Masimo.

12.3 Responsible Parties

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

13 ADMINISTRATIVE ASPECTS

13.1 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.

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 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.

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 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.

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

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

It specifies general requirements intended to:

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

The Principal Investigator of the clinical investigation shall:

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

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

15 REVISION HISTORY:

Version Number	Version Date	Summary of Revisions Made:
1.0	10/25/18	Original version
2.0	01/31/19	5.3 Updated exclusion criteria to "Jaundice or hyperbilirubin" [redacted]

16 REFERENCES

1. Jubran, A. (2015). Pulse oximetry. *Crit Care*, **19**, 272.
2. Miller, S.P., MD; McQullen, P.S., MD; Hamrick, S., MD; Xu, D., PhD; Glidden, D.V, PhD; Charlton, N., BS; Karl, T., MD; Azakie, A., MD; Ferriero, D.M., MD; Barkovich, A.J., MD; and Vigneron, D.B., PhD. (2007). Abnormal brain development in newborns with congenital heart disease. *N Engl J. Of Med.*, **357**, 1928-1938.
3. Ricard, C.A., Dammann, C.E.L., and Dammann, O. (2017). Screening tool for early postnatal prediction of retinopathy of prematurity in preterm newborns (STEP-ROP). *Neonataology*, **112**, 130-136.
4. Shahidullah, M., Dey, A.C., Ahmed, F., Jahan, I., Dey, S.K. Choudhury, N., and Mannan, M.A. (2017). Retinopathy of prematurity and its associate with neonatal factors. *Bangabandhu Sheikh Mujib. Med. Univ. J.*, **10**, 1-4.
5. Mouledoux, J., MD, MSCI; Guerra, S., RN, BSN,; Ballweg, J., MD; Li, Y., MD; and Walsh, W., MD. (2017). A novel, more efficient, staged approach for critical congenital heart disease screening. *J Perinatol*, **37**, 288-290.
6. Booth, Dukatz, Ausman, and Wider. "Cerebral and somatic venous oximetry in adults and infants." Surg. Neurol Int. 2010; 1: 75.
7. 2. Colak Z, Borojevic M, Bogovic A, Ivancan V, Biocina B, Majeric-Kogler V. Influence of intraoperative cerebral oximetry monitoring on neurocognitive function after coronary artery bypass surgery: a randomized, prospective study. European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery. 2015 Mar;47(3):447-54.
8. 3. Slater JP, Guarino T, Stack J, et al. Cerebral Oxygen Desaturation Predicts Cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg. 2009;87:36-45.
9. 4. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. The heart surgery forum. 2004;7(5):E376-381.
10. 5. Deschamps A, Lambert J, Couture P, et al. Reversal of decreases in cerebral saturation in high-risk cardiac surgery. Journal of cardiothoracic and vascular anesthesia. 2013;27(6):1260-1266