Official Title: Evaluation of Non-Invasive Hemoglobin in Trauma Patients

Date of Protocol: 04 August 2016

NCT Number: NCT03123328

Evaluation of Non-Invasive Hemoglobin in Trauma Patients

Sponsor: Masimo
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Irvine, California 92618

Principal Investigator: [redacted]

Study Devices:
Masimo Radical 7 Pulse CO-Oximeter
Masimo Rainbow SpHb Sensors
Laptop with data collection software

Sponsor Protocol Number: HOLC0001

IRB: HSC-GEN-15-0343
University of Texas Health Science Center at Houston
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Revision History:

Version Number	Version Date	Summary of Revisions Made:
1	March 23, 2016	[redacted]
2	July 21, 2016	[redacted]

1 INTRODUCTION

This document is a protocol for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with 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

The accurate measurement of circulating blood hemoglobin (Hgb) levels is one of the cornerstones of optimal treatment for traumatic injury and severe hemorrhage, the leading cause of death in people 1 to 40 years of age. In an autopsy study from the conflicts in Iraq and Afghanistan, fully 86% of all potentially preventable deaths were from truncal hemorrhage [Kelly 2008]. Likewise, in the civilian arena, the leading cause of potentially preventable death is early truncal hemorrhage [Demetriades 2004], with most deaths occur occurring within 6-12 hours of admission [Holcomb 2008, Clarke 2002, Moore 2008]. Measurement of Hgb requires blood to be drawn and subjected to laboratory analysis, resulting in delays of up to one hour before data are returned. This time lag can be critical in patients who have internal bleeding, a situation which can be difficult to detect even for an experienced clinician. Despite conventional teaching, the Hgb levels do change rapidly, and the first Hgb on admission to the hospital is highly predictive for blood loss. Thus, a portable, accurate, rapid, noninvasive measurement system is needed to improve quality and efficiency of treatment. In 2012, a study was conducted at Memorial Hermann Hospital (MHH) to evaluate Masimo's Radical-7, a non-invasive pulse co-oximeter, for Code 3 (highest acuity status) trauma patient during the first twenty four hours following patient presentation to the Emergency Department. One parameter measured by the device was the non-invasive Hgb (SpHb) and was compared to any laboratory Hgb (tHb) that was available for clinical care. The results of the study were recently published and it was found that while SpHb technology showed promise, it still required further refinement in order to be used for management of severely injured trauma patients [Moore 2013]. Since the conclusion of that study, the technology has continued to improve and the latest SpHb sensor revision has been designed to provide more accurate values in cases of varying oxygen saturation and in cases of large fluctuations in peripheral perfusion; the latter is often a compensatory or medically- induced physiological response which is often seen in trauma patient. Furthermore, a better understanding of the factors that may affect measurements of both tHb and SpHb may decrease inter-measurement variability and further improve the previously published performance.

1.2 Study Devices

Masimo pulse CO-Oximeter: Radical-7 is an FDA-cleared pulse CO-Oximeter handheld used for noninvasive and continuous monitoring of several physiological parameters including total hemoglobin concentration. It consists of a portable handheld device and a docking station for charging and transferring data. The docking station used in this study has been upgraded to allow transfer of high resolution wavelength data through a serial cable that is connected to a laptop.

Masimo Rainbow sensors: a finger probe that consists of a series of light emitting diodes (LEDs) and photodetectors. First, light is emitted through a capillary bed; then, the sensors detect the transmitted light. The signals from the sensor are processed and used to quantify hemoglobin levels. Masimo Rainbow sensors for the measurement of hemoglobin are FDA-cleared for use on adults.

Laptop [redacted]

1.3 Risk/Benefits

There will be no direct benefits to the enrolled patients. Future benefits to patients might include a reduction in blood draws and possibly optimized fluid management to the ability to trend moment-by-moment hemoglobin levels in trauma patients. No compensation will be paid to the participants or their families.

The risk from the device is minimal since it is non-invasive and uses wavelengths in the red and near infrared range like a conventional pulse oximeter used in routine clinical practice for over 15 years but can include skin irritation and thermal skin burn from the optical sensors.

2 STUDY HYPOTHESIS

SpHb can be used to identify bleeding patients sooner than standard of care by identifying critical drops between laboratory samples.

3 STUDY DESIGN

This is a prospective, non-blinded, non-randomized, non-interventional study of the Masimo pulse oximeter and sensors in a trauma setting.

4 CLINICAL TEST SITE

Center for Translational Injury Research
University of Texas Health Science Center at Houston
6410 Fannin, UTPB 1100.00
Houston, TX 77030

[redacted]

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

Up to 600 patients will be enrolled to obtain a minimum of two paired data points on 150 subjects.

5.2 Inclusion Criteria

- Estimated 16 years of age or older or greater than or equal to 50 kg body weight if age unknown. (Adult trauma population includes patients 16 years of age and over at MHH).
- Level 1 (highest trauma activation) status at time of arrival to emergency department (ED).
- Expected to be admitted to the ICU/IMU for in hospital care.

5.3 Exclusion Criteria

- Moribund patients with devastating injuries and expected die within one hour of ED admission.

- Prisoners, defined as those who have been directly admitted from a correctional facility (Prisoners are excluded because of their vulnerable population status. A free living individual who is under police observation as a suspect will remain in the study until hospital discharge).
- Obvious pregnancy in the ED (Pregnant women have a significantly increased intravascular volume and physiologic reserve for bleeding which can require adjustments to the standard treatment protocols therefore for consistency for analysis, pregnant women will be excluded).
- Received greater than 5 minutes of cardiopulmonary resuscitation (CPR) in the pre-arrival or hospital setting. (Patients who receive greater than 5 minutes of CPR are more likely to have non-survivable injuries and not likely to be admitted to the ICU for care).
- Has, on the ring, middle and index fingers of both hands, any of the following: finger deformities, injuries including burns, scar tissue or infection, or any material that may interfere with sensor application or trans-illumination of the site.
- Has significant bilateral trauma to the arms or forearms

5.4 Subject Recruitment and Screening

Upon presentation to the Emergency department, the clinical research staff will screen patients to determine eligibility based on the inclusion/exclusion criteria above. Patients who satisfy eligibility criteria will be enrolled.

5.5 Informed Consent Process

The study will be conducted utilizing a waiver of informed consent.

6 STUDY DEVICES

Masimo Radical 7 pulse CO-Oximeter

Masimo Rainbow SpHb Sensors

Laptop [redacted]

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

7.1 Study Procedures

Data collection will begin immediately within the first few minutes after admission to the emergency department. The SpHb butterfly sensor will be placed according to instructions in the manual of operations, [redacted] and connected to a time-synchronized Masimo Radical-7. Sensor placement will occur after the patient's position has been stabilized and after the secondary survey has been completed. The sensor will be placed, in order of preference, on the ring or middle finger of the non-dominant hand, the ring or middle finger of the dominant hand, the index finger of non-dominant hand, the index finger of the dominant hand. The sensor will not be placed on the thumb or the small finger, nor shall it be placed on any other location on the patient's body. The measurement site must be clean, have no deformity with any part of the finger including nail bed and have no trauma on the arm or forearm proximal to the site of sensor placement.

7.2 Study Duration

The Masimo Radical-7 will remain on the subject for up to the first 24 hours following ED admission or discharge from the ICU/IMU (whichever comes first). Direct subject observation will continue until 1) subject has arrived to the ICU/IMU following ED admission, 2) the subject expires or 3) 24 hours following ED admission or discharge from the ICU/IMU (whichever occurs first). Once direct observation is complete, the research team will continue to monitor the subject admitted to ICU (and had first a.m. lab draw completed) throughout the hospitalization to assess for additional procedures and complications incurred. For subjects who are not admitted to ICU/IMU and do not have a second sample drawn, additional data will be obtained through the trauma registry.

7.3 Sample Collection

Blood samples will be collected at time of ED admission and first a.m. lab draw in ICU. The blood samples will be based on clinical need and sent to at least two reference devices: the standard of care reference device for patient, hospital laboratory devices located at MHH, and a cyanomethemoglobin (HiCN) analyzer and a hematology analyzer located at a Masimo facility. For those subjects who have laboratory tests ordered at time of ICU admission, a third sample will be collected and sent to the CeTIR research lab for preparation for the cyanomethemoglobin analyzer at a Masimo facility. The collection of the HiCN and hematology analyzer samples must follow standard laboratory practices for handling of blood products as detailed in the manual of operations with at least 1 mL of blood being collected in an EDTA tube. Each sample will have a unique identifier with the identification key revealed by the site only after the sample has been processed by the Masimo analyzer. The exact time of sampling will be documented for retrospective analysis along with type (venous or arterial) and site of blood sampling, location of patient, time since presentation, and specific hospital laboratory analyzer used.

7.4 Data Collection

While the patient is in the Emergency Room, data will be collected and stored on a Radical-7. In the operating room and intensive care unit, data collection will be done using a Radical 7 connected to a laptop computer which will store live data [redacted]. All data will be properly labeled and downloaded to a server as soon as it is available for retrospective analysis.

Information to be collected will come from the trauma registry and medical records and will include subject demographics (gender, age, race/ethnicity), injury details (type of injury, severity, location on body), pre-hospital EMS care, initial ED care (blood products, life- saving interventions, vital signs), surgical and interventional radiology procedures, major complications (i.e. ARDS, sepsis, MOF), discharge location, number of hospital, ventilator and ICU days, and quantity and timing of blood product administration, anesthetics, changes in oxygenation, blood pressure cuff location, notes about any movements during surgery.

7.5 Data Analysis

This trial will provide baseline data on the performance of SpHb in a population with expected rapid changes in tHb levels. The primary metric to be measured is SpHb's ability to detect critical drops in a trauma population and present the data in a categorical table; statistical significance will be calculated with chi-squared analysis.

The secondary metrics that will be calculated include:

1- "Trend capability," which will be determined by calculating the regression equation and coefficient of determination of a linear mixed effect regression model. The relative differences between data points will be represented graphically with polar plots [Critchley] and 4 quadrant plots.
2- Performance of different devices compared to HiCN values (the gold-standard for measuring hemoglobin concentration in blood), including the variability caused by standard of care laboratory devices.
3- Absolute accuracy calculation, which will be done by mean test method error with standard deviation, average root mean squared and graphically through Bland-Altman plots [Bland].

Analysis will be performed on the pooled data set as well as separate analyses on all data with high or low signal confidence respectively.

A total of 150 subjects with at least 2 blood samples will be included in the analysis. As a critical drop would require at least two laboratory data points for reference, the study will be powered in order to be 90% confident of achieving that target knowing that 47% of patients recruited in the previous study had at least two paired data points and that it is expected that 20% of patients will be excluded after enrollment (no data points).

An interim analysis will be performed after 50 cases with at least 2 blood samples per case have been completed. This will allow determination of the final sample size in order to obtain an appropriate definition of critical drop detection. The final sample size may be adjusted as a result of this analysis.

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, and unanticipated adverse device effect are provided below (ISO 14155:2011, 21 CFR 812.3(s)).

- Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
- Adverse Device Effect (ADE): an adverse device effect is any untoward or unintended response to a medical device which may result from insufficiencies in the instructions for use or deployment of the device, or from use error.
- Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.
- Serious Adverse Device Effect (SADE): a serious adverse device effect is an adverse device effect that results in death, inpatient hospitalization, severe or permanent disability or is life threatening.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life threatening problem or death cause by or associated with, a device, if the effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan, or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects. Refer to the Device Risk Analysis and Risk Assessment section for details on anticipated adverse device effects.

8.2 Anticipated Adverse Events:

The risk from the device is minimal since it is non-invasive and uses wavelengths in the red and near infrared range like a conventional pulse oximeter used in routine clinical practice for over 15 years but can include skin irritation and thermal skin burn from the optical sensors.

8.3 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.

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.

9 DOCUMENTATION AND DATA MANAGEMENT

9.1 Screening and Enrollment Log

A subject screening and enrollment log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

9.2 Case Report Forms

The site shall contain study data in a Case Report Form for each subject enrolled, completed and the CRF will be 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.

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 study. A copy of the completed and signed CRFs will remain on site.

9.3 Data Collection, Transfer and Storage

9.3.1 Device data will be captured through data capture software (PulseOx Automated Data Collection) and stored on a laptop. Device data, along with electronic copies of the CRFs, will be uploaded to sponsor via secure FTP portal after each study visit completion.

9.3.2 Only authorized sponsor personnel will have access to transferred data. Once data has been transferred via FTP, they are moved from FTP server to a secure and backed drive. Device data and CRF 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.

9.4 Record Retention

Study data will be retained for the necessary period of time as required by the institution's regulations. Study Records shall be retained for a minimum of two years after study closure. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

10 MONITORING PLAN

10.1 As the sponsor of this clinical investigation, Masimo Corporation is required by 21 CFR, Part 812, of the Food and Drug Administration regulations to monitor and oversee the progress of the investigation. The monitor(s) assigned by Masimo Corporation to this task will be a direct employee from the Clinical Research department trained on departmental SOPs on conduct and monitoring of sponsored studies.

10.2 In accordance with good clinical practices guidelines, there will be at least three scheduled monitoring visits to ensure overall regulatory compliance of the study:

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment.
- At least one monitoring visit during enrollment, when about 10-15% done and/or every year.
- A final close out visit after the last patient had finished the study.

10.3 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.

10.4 It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency and accuracy of the data being entered on them.

10.5 During each visit, the monitor will also verify presence of informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs/SADEs and protocol deviations/violations, and check CRF against source documentation.

10.6 After each visit, the monitor will provide a monitoring report to the investigator within 4 weeks of visit completion. The monitoring report will detail findings and open action items observed during the visit. It is the responsibility of the Principal Investigator and Study Coordinator(s) to respond to the findings of the monitoring report, and complete any open action items as soon as possible but no later than 60 days of receiving the monitoring report. Any open action items not completed within the time allowed may be sufficient grounds for study site suspension or termination; it will be up to the sponsor to determine whether any incomplete action items are sufficient grounds for suspension or termination. See Section 16 for details on suspension and termination.

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

11 ADMINISTRATIVE ASPECTS

11.1 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.

11.2 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.

11.3 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 determines that the study site's compliance to be inadequate at any point during the study, and sponsor moves 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 upon provision of 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. The sponsor may resume the terminated clinical investigation with prior IRB approval if the device is non-significant risk.

11.4 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.

12 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.

13 REFERENCES

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