Evaluation of Physiological Variables and Detection of Blood Loss in Healthy Adults with Different Subject Positioning by the Zynex Cardiac Monitor, Model 1500 (CM-1500)

NCT#: 05980013

Date: 08-APR-2025

CLINICAL PROTOCOL

TITLE	Evaluation of Physiological Variables and Detection of Blood Loss in Healthy Adults with Different Subject Positioning by the Zynex Cardiac Monitor, Model 1500 (CM-1500)
PROTOCOL	ZMS-1500-Pa2023
SPONSOR	Zynex Monitoring Solutions (ZMS) 9555 Maroon Circle Englewood, CO 80112
PROTOCOL VERSION	1.0
DOCUMENT REVIEW & APPROVAL	

Sponsor Representative: [redacted]
Don Gregg
President, Zynex Monitoring Solutions

Sponsor Representative: [redacted]
Brianne Orona, PhD
Medical Science Liaison

PROTOCOL SIGNATURE PAGE

TITLE	Evaluation of Physiological Variables and Detection of Blood Loss in Healthy Adults with Different Subject Positioning by the Zynex Cardiac Monitor, Model 1500 (CM-1500)
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The signature below constitutes I have read, understood, and the approve this protocol and provide assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding subject confidentiality, and according to local legal and regulatory requirements, including all applicable U.S. federal and local regulations and ICH guidelines.

I agree to supervise all testing of the device involving human subjects. I confirm I will ensure Informed Consent requirements will be met for all subjects. I confirm I will ensure Informed Consent of each subject is obtained before any study procedures; protect the rights, safety, and welfare of all study subjects; prepare and maintain accurate, current, and complete records (including Adverse Events); provide timely reports to the Sponsor; ensure changes are not implemented without prospective IRB approval unless required to eliminate an immediate hazard to subjects; retain records as set out in the protocol; disclose relevant financial information.

Principal Investigator (PI): Dr. Debra Smith, MD PhD

PI Printed Name

[redacted]

PI Signature

[redacted]

Date (DD-MMM-YYYY)

CONFIDENTIALITY STATEMENT

This document is the confidential information of Zynex. It is provided to you as an investigator or consultant for review by you, your personnel, and the applicable Institutional Review Board/Ethics Committee. Your acceptance of this document constitutes an agreement that you cannot disclose the information contained herein to others without the prior written consent of Zynex.

PROTOCOL AMENDMENT HISTORY

Version Number	Description of Change(s)	Reason for Change
1.0	Initial protocol; no changes	N/A

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FIGURES AND TABLES

1 INTRODUCTION

Intraoperative and postoperative hemorrhage incidence can vary depending on the type of surgery and can lead to severe clinical complications ranging from mild anemia to fatal hemorrhagic shock. Those that recover from severe hemorrhagic events often have poor functional outcomes and are at risk for greater long-term mortality. Numerous studies reveal that post-operative hemorrhagic events are also quite frequent, occurring in as many as 13 to 19% of patients following various type of surgeries (i.e., major pancreatic resections, transoral robotic surgery (TORS) for oropharyngeal squamous cell carcinoma, and living-donor transplants). Hemorrhagic shock is also a leading cause of death in trauma.[1-6]

Monitoring and detecting fluid changes in patients can be complicated. Physiological responses associated with hemorrhagic events are often delayed because of compensation mechanisms that act to sustain blood pressure and protect tissue perfusion.[1] The ability to continuously and non-invasively detect changes in central blood volume and blood loss will permit appropriate hemodynamic management during events at high risk for acute blood loss such as surgery, trauma, post-operative care and other therapeutic procedures. Through early detection and improved hemodynamic monitoring, optimization of fluid balance, anesthesia titration, and augmenting other acute care management requirements, a clinician should be able to improve overall patient stability, minimize complications, diminish surgical trauma and reduce recovery time.

Current methods for acutely monitoring blood volume and blood loss include monitoring of vital signs (such as heart rate, blood pressure, respirations, and oxygen saturation), invasive central venous (right heart central venous pressure measurement and Swan-Ganz pulmonary capillary wedge pressure measurements) and arterial catheters designed to monitor hemodynamic status centrally. Vital sign monitoring may not indicate small amounts of acute blood loss and arterial and venous cannulations can create insertion complications such as perforations in the vasculature, pneumothorax, arrhythmias, thrombosis and infection. While invasive central monitoring may provide extremely accurate information, changes may not be good indicators of early central hypovolemia or with smaller blood volume reductions[1-2]. New non-invasive technologies have recently become available but often include many physiological parameters that may require expedited clinical interpretation in high stress environments and have not become well-established.

The Zynex Cardiac Monitor, Model 1500 (CM-1500) uses a relative patient standard approach by non-invasively and simultaneously monitoring five (5) physiological parameters, including bioelectrical impedance, electrocardiogram (ECG) amplitude, photoplethysmogram (PPG) amplitude, heart rate (HR), and skin temperature. The CM-1500 starts by creating a baseline for each patient in a normal state. When the monitoring session starts, each patient starts with a Relative Index (RI) of 100, signifying the collection of parameters near their original baseline value(s). The Relative Index value acts as a combinational score for all the parameters indicative of relative fluid change.

1.1 CLINICAL RATIONALE

The proposed clinical study is designed to examine whether subject positioning has an effect on how the CM-1500 individual parameters and Relative Index change in response to small blood volume changes in

healthy individuals consented to undergo a 1-unit blood draw (approx. 500mL). An initial feasibility study was conducted (n = 12 subjects) to confirm that the CM-1500 can be used to track acute blood loss in healthy individuals donating 500mL of blood in the supine position. Additional studies are being conducted in various healthy volunteer and clinical settings to characterize RI performance when known volumes of fluid are removed.

2 INVESTIGATIONAL PLAN

2.1 OBJECTIVES

The primary objective of the study is to examine the effects of subject positioning on the ability of the CM-1500 parameters to detect minor blood loss.

Exploratory objectives of the study will include:

- Compare the performance of the CM-1500 monitoring during a whole blood donation with subjects positioned in either a fully supine position (180°) or in a reclined position (approx. 135°)
- Investigate any possible correlations between adverse events, subject demographics, changes in the individual parameters, and timing of when the events occurred.

2.2 STUDY DURATION

Enrollment in the study is expected to take approximately five (5) months, and data analysis may take up to an additional two (2) months to complete.

2.3 STUDY DESIGN

The study is a prospective, non-randomized, non-blinded, non-significant risk study enrolling up to 60 healthy adult subjects consented to undergo a 1-unit whole blood draw procedure.

The present study will involve enrolling subjects that will undergo blood draw wearing the study device (CM-1500) and capture study-required physiological parameters pre-, during, and post-donation.

2.4 STUDY ENDPOINTS

The study endpoints include the change and percentage of change between measurements before and after blood draw in the Relative Index, individual parameters and standard physiological parameters. The change is defined as the value after draw minus the one before draw. The percentage of change is the change value divided by the value before draw. Other endpoints such as area under receiver operating characteristic (ROC) together with sensitivity and specificity at various thresholds are also derived for the Relative Index, individual parameters and each of standard physiological parameters in detecting in detecting minor blood loss (i.e., ~500mL).

3 STUDY DEVICE

3.1 CARDIAC MONITOR, MODEL 1500 (CM-1500)

3.1.1 DEVICE DESCRIPTION

The CM-1500 is a U.S. Food and Drug Administration (FDA) cleared non-invasive monitoring device that simultaneously monitors five (5) parameters of a patient's body. Parameters include bioelectrical impedance, heart rate, ECG amplitude, PPG amplitude, and skin temperature. A combination of these parameters is represented by a single number known as the Relative Index value. This value is indicative of relative changes in fluid volume. The Relative Index (RI) is a unique functionality of the Zynex Cardiac Monitoring Device.

3.1.2 DEVICE DESIGN AND COMPONENTS

The CM-1500 is an all-inclusive device that includes the following components: display monitor (1), power supply (1), trunk cable (1), wrist cuff with attached PPG finger glove (1), wrist strap (1), and electrode array set (2). The wrist cuff with attached PPG finger glove may be cleaned and reused. The wrist strap is single-subject use. The electrode array sets are single-use, single-subject.

3.1.3 PRINCIPLES OF OPERATION

The CM-1500 measures bioelectrical impedance (ohms), heart rate (BPM), ECG amplitude (mV), PPG amplitude, and skin temperature (°C or °F). As parameters change towards indications of fluid change/imbalance, the Relative Index, which acts as a combinational score of percent change values for all of the parameters, will compound these changes into a singular value to signify overall fluid changes/imbalances within the patient's body. When the monitoring session starts, every patient will start with a Relative Index of 100, signifying the combination of physiological parameters is near or at their original baseline values for all five monitored parameters. All parameters are continuously measured and tracked during a monitoring session. ECG and PPG amplitude values are only visible on the Advanced monitoring session display mode, as selected in the Setup screen.

3.1.4 INDICATIONS FOR USE

Per the device's FDA clearance, the CM-1500 is indicated for monitoring bioelectrical impedance, heart rate, ECG amplitude, and PPG amplitude and their relative changes, indicative of relative changes in fluid volume in adult patients.

3.1.5 INTENDED USE

Per the device's FDA clearance, the CM-1500 is intended to be used in professional medical environments, i.e., hospitals, clinics, and research institutions. The CM-1500 is a standalone device intended for desktop use, where device operation is to be performed as uninterrupted patient monitoring. The CM-1500 shall only be used by a qualified device operator. The operator shall have knowledge of the system and data interpretation obtained via medical education, system documentation, and specific courses. The device does not report any diagnosis but provides numerical values; it is ultimately the physician's responsibility to make proper diagnosis and judgments based on these values.

4 SUBJECT POPULATION AND SELECTION

4.1 POPULATION AND ANTICIPATED NUMBER OF SUBJECTS

Up to 60 healthy adult subjects who meetthe inclusion and exclusion criteria will be enrolled in the study. A minimum of 20 subjects will be enrolled at each of the subject positionings (180° and 135°). Every reasonable effort will be made to achieve a 50:50 split between the two subject positionings.

4.2 SUBJECT INCLUSION CRITERIA

- I.1 Ability to provide written informed consent
- I.2 Ability and willingness to comply with the study procedures and duration requirements
- I.3 18 years of age or older
- I.4 Consented and eligible to undergo a single unit whole blood donation

4.3 SUBJECT EXCLUSION CRITERIA

- E.1 Females who are pregnant or breastfeeding
- E.2 Undergone an amputation of any upper extremity
- E.3 Diagnosed with dextrocardia
- E.4 Subjects who have a pacemaker
- E.5 Subjects with body hair density which prevents adequate application of device electrodes

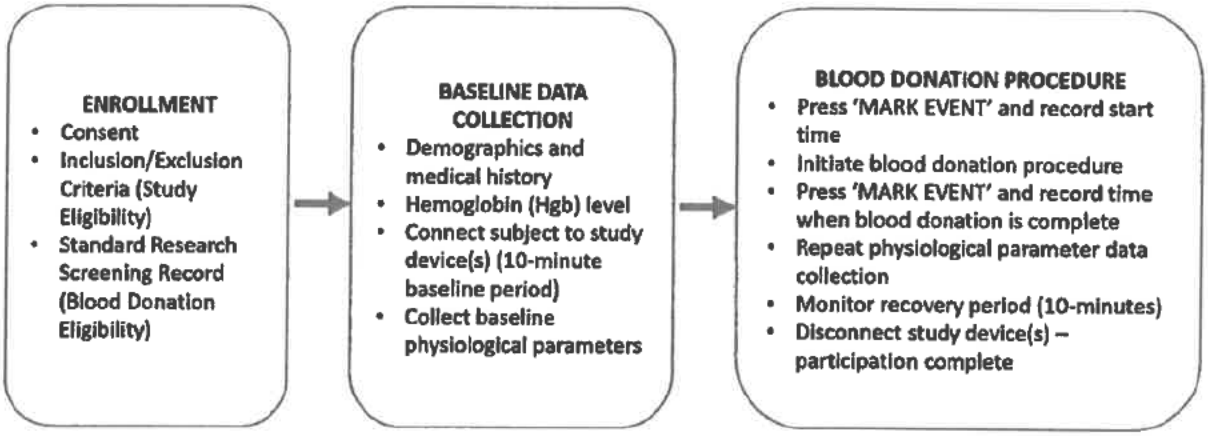
4.4 SUBJECT WITHDRAW / EARLY TERMINATION

Subjects who withdraw from the study before using the CM-1500 will be replaced. The reason the subject withdrew from the study may be recorded; subjects are not required to provide a reason. Subject withdrawal / early termination criteria may include but are not limited to:

- W.1 Subject requests to be withdrawn from the study or withdraws consent.
- W.2 Subject refuses to comply with required study procedures.
- W.3 An Adverse Event ("AE") makes the continuation of the subject impossible or inadvisable
- W.4 The Investigator determines it is in the subject's best interest to discontinue from the study.

5 STUDY PROCEDURE

Figure 1: Procedure Overview



5.1 ENROLLMENT

A subject will be considered enrolled in the study after providing written informed consent. Subjects will only be eligible to participate in the study if they have consented to undergo a 1-unit whole blood draw procedure. Enrollment in the study is anticipated to take a subject approximately 60-90 minutes.

5.1.1 INFORMED CONSENT

The Investigator or qualified designated study personnel will complete the Informed Consent process before any study procedures may occur. The subject will be provided an IRB-approved version of the Informed Consent Form (ICF). The subject will have an ample amount of time to read the ICF and ask questions before providing written consent. The subject will receive a signed copy of the ICF. The Investigator or qualified designated study personnel will record that consent was obtained prior to performing study procedures.

A subject who has signed an Informed Consent but is found to ultimately not meet eligibility criteria prior to the blood draw will be classified as "Consent Ineligible". There are no follow-up or reporting requirements for consent ineligible subjects. They do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file.

5.2 DEMOGRAPHIC AND BASELINE DATA

Demographic and enrollment data collection will include capturing health screening data on a case report form (CRF). These data will include but are not limited to skin tone, smoking history, a blood donation anxiety questionnaire, blood donation history, and if subjects are currently taking any medications or supplements that could impact their physiological response to the blood draw procedure. Female subjects will self-report they are not currently pregnant or have been pregnant in the previous six (6) weeks.

Baseline hemoglobin will be collected as part of a standard blood draw procedure via a finger stick (or per standard of care for the site). Subjects that are unable to proceed with the blood donation due to their baseline hemoglobin level will be consent ineligible.

Following demographic and enrollment data collection and PRIOR to blood donation, all subjects will be connected to the CM-1500 per the Instructions for Use. Designated study personnel must ensure that the subject ID number and gender is entered for each subject prior to starting a new monitoring session.

The CM-1500 will be connected to the subject's left side of the body. Once the needle stick has been completed but the line is clamped to prevent premature blood draw, the subject's chair should be adjusted to the position assigned upon enrollment. The monitoring session should then start with the subject placed in the designated position for a minimum of ten (10) minutes before the baseline measurements will be recorded. Just prior to the blood draw, a skin temperature recording should occur on the left dorsal wrist.

5.3 SUBJECT PARTICIPATION

Subjects will proceed with the blood draw procedure wearing the CM-1500 on the left arm. For this protocol, blood draws can only occur on the right arm. Subjects will remain in their assigned position for the entirety of the procedure unless position change is required in response to a subject reaction. Immediately prior to the start of the blood donation procedure, the Investigator or designated study personnel will press the 'MARK EVENT' button on the CM-1500 and record the local time on the CRF which will signify the start of the procedure on the device.

The Investigator or designated study personnel will monitor the subject per standard of care throughout the procedure and record any adverse events noted. Total amount of blood collected will vary per subject based upon their estimated blood volume, and the final amount drawn will be recorded.

Immediately following completion of the blood donation, the Investigator or designated study personnel should press 'MARK EVENT' on the CM-1500 and record the local time on the CRF. Skin temperature from the left dorsal wrist should again be measured at this time.

Subjects will remain connected to the CM-1500 for at least ten (10) minutes following the donation procedure. Following the 10-minute post-donation monitoring period, subjects will be disconnected from the study device, and study participation will be complete.

5.4 ADVERSE EVENTS

Adverse Events (AE), Serious Adverse Events (SAE), or Unanticipated Adverse Device Effect (UADE) that occur after informed consent and before completion of the study will be recorded. SAE's may require follow-up contact via a telephone call, depending on the nature of the SAE.

5.5 SUBJECT COMPLETION

Subjects' participation in the study will be considered complete once the monitoring session has ended and the device has been removed.

6 DEVICE MANAGEMENT

6.1 UNPACKING AND INSPECTION

It is the responsibility of the Principal Investigator (PI) to ensure that all study devices are unpacked and inspected prior to using in any study procedures. Upon arrival, the Investigator or designated study personnel will remove the device display monitor and accessories from the shipping container; ensure all device components are received. The study site must inform the Sponsor of any missing or damaged items within seven (7) days. Devices with any missing or damaged items cannot be used and shall be replaced.

6.2 ACCOUNTABILITY, STORAGE & DISPENSATION

It is the responsibility of the Principal Investigator to ensure all study devices are inventoried and accounted for throughout the conduct of the study. The Investigator or qualified designated study personnel will record all information on the Device Accountability forms maintained in the Investigator Site Files (ISF).

The investigational device will be stored at the study center. When not in use, the device will be stored in a secure location (i.e., area with limited access or in a locked cabinet) under appropriate environmental conditions found in the Instructions for Use (IFU) manual.

The study device shall only be used under the supervision of the Principal Investigator or designated study personnel on authorized study subjects.

6.3 CLEANING & RETURN

The study devices shall be cleaned before each use. Cleaning procedures will be followed per the Instructions for Use (IFU) manuals. The study devices and any unused accessories will be returned to the Sponsor after study completion.

7 RISKS & BENEFITS

7.1 RISK DETERMINTATION & REDUCTION

This study is determined to be non-significant risk. An Investigational Device Exemption will not be submitted based on this determination.

Study subjects are subject to risk no greater than or similar to risks associated with undergoing a standard blood donation. The use of the CM-1500 does not meet the definition of significant risk under 21CRF 812.3 (m). All adverse events will be recorded and analyzed to evaluate their significance. Possible risks may include:

- [Possible, Rare] Skin irritation could occur from the electrodes
- [Possible, Mild] Discomfort could occur due to lying in a supine position for duration of the donation procedure.

Every possible effort will be made to reduce the risks to a minimum. Investigators or qualified designated study personnel will be experienced and skilled in blood donation procedures, receive training on the protocol and use of the device. All adverse events will be documented and reported to the Sponsor.

7.2 BENEFITS

This study is for research purposes only. There is no direct benefit to subjects participating in the study. Information from this study may help other people in the future.

8 SAFETY ASSESSMENT AND MANAGEMENT

Safety will be assessed by reviewing and summarizing adverse events.

8.1 SAFETY DEFINITIONS

8.1.1 ADVERSE EVENT (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence, whether or not related to the study device or study procedure. AE's are characterized by grading, actions taken, relationship to donation or study procedure, and outcome. These definitions are in the corresponding tables below. All adverse events related to the blood donation procedure will be recorded and reported in addition to those that may occur specific to the protocol-defined study procedure. All attempts should be made to ensure resolution of the adverse event upon study completion.

Table 1: Adverse Event Severity Grading

Severity	Description
Grade 1: Mild	Awareness of signs or symptoms, but they are easily tolerated
Grade 2: Moderate	Enough discomfort to cause interference with usual activity
Grade 3: Severe	Incapacitating, with the inability to work or do usual activity
Grade 4: Fatal	Subject expired/death occurred

Table 2: Adverse Events Action(s) Taken

Action Taken (Check all that apply)	Description
None	No actions were taken, observation only.
Medications	Subject required medication(s)
Other Treatment	Subject required other treatment(s)
Early Withdrawal	Adverse event led to early study withdrawal

Table 3: Adverse Event Relationship to Blood Draw or Study Procedure

Relationship	Description
None	Causal relationship can be ruled out
Possible – Donation Procedure	Causal relationship is reasonably possible to the blood draw procedure (i.e., the relationship cannot be ruled out)
Possible – Study Device	Causal relationship is reasonably possible to the study device (i.e., the relationship cannot be ruled out)
Yes – Donation Procedure	Causal relationship to the blood draw procedure is certain
Yes – Study Device	Causal relationship to the study device is certain

Table 4: Adverse Event Outcome

Outcome	Description
Recovered/Resolved	Subject recovered and event was resolved upon study completion
Recovered/Resolved with Sequelae	Subject recovered but exhibited lingering minor symptoms upon study completion
Recovering	Adverse event persisted upon study completion but was improving
Not Recovered	Adverse event persisted upon study completion and was not exhibiting any signs of improvement
Death	Subject expired
Unknown	Status of the adverse event was unknown upon study completion

8.1.2 SERIOUS ADVERSE EVENT (SAE)

An SAE is defined as an AE that meets any of the following criteria: Fatal or life-threatening*; requires or prolongs in-subject hospitalization**; results in persistent or significant disability/incapacity; congenital anomaly/birth defect; important medical event. An event's severity grading, action(s) taken, relationship to the donation or study procedure, and the outcome will all be used for SAE's.

*Life-threatening is defined as an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically may have caused death if it was more severe.

**In-subject hospitalization is defined as an event in which the subject was admitted to the hospital for one or more days, even if released on the same day or an emergency room visit, which results in admission to the hospital. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes criteria.

8.1.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An unanticipated adverse device effect is defined by 21 CFR 812.3 as any serious adverse effect on the health of safety or life-threatening problem or death caused by or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including supplementary plan or application, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of

subjects. The Investigator or designee will indicate if they believe an event was an unanticipated adverse device effect on the case report form, and the Sponsor will evaluate for reporting requirements defined below.

8.2 SAFETY REPORTING

Safety reporting begins at the time of signed Informed Consent and ends at subject study completion.

Investigators shall submit to the Sponsor a report of any AE's or SAE's that occur during the study within five (5) working days but no later than ten (10) days after the Investigator learns of the event.

Investigators shall submit to the Sponsor a report of any UADE(s) that occur during the study as soon as possible but no later than five (5) working days after the Investigator learns of the effect. Sponsors will evaluate UADE's.

8.2.1 REPORTING EVENTS & SAFETY CONTACTS

Events will be reported, in writing, to the Sponsor as soon as possible but no later than five (5) working days after the Investigator learns of the event. In an event resulting in the death of the subject, the event will be reported within 24-hours of knowledge of the event. The Sponsor is responsible for fulfilling IRB and regulatory reporting requirements.

Table 5: Study Reporting Contacts

Contact	Contact Information
Sponsor Representative	[redacted]
IRB	[redacted]
Mailing Address	[redacted]

9 STATISTICAL METHODS AND CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

This study is designed as a feasibility study to evaluate the effect of subject positioning on the individual parameters and Relative Index (RI) during minor blood loss in the form of a 1 unit (~500mL) whole blood draw. No statistical hypotheses have been generated for this study; therefore, the sample size of up to 60

participants is empirically determined to be sufficient for an early-phase hypothesis-generating study and is based on clinical judgment rather than statistical considerations.

9.2 DATASETS ANALYZED

All eligible subjects who were enrolled in the study and connected to the study devices will be included in the analyses. Subjects who withdraw after enrollment and before the study devices are connected will be excluded from the analyses.

9.3 STATISTICAL ANALYSIS

9.3.1 DESCRIPTIVE STATISTICS

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, quartiles, minimum, maximum, and number of observations, unless otherwise specified. Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency count, and percentage. Percentages will be calculated using n as the denominator.

9.3.2 STATISTICAL METHOD FOR CONTINUOUS VARIABLES

The normality of continuous data will be assessed both visually and by Shapiro-Wilk test. If data are considered normally distributed, the 95% CI of the mean will be constructed based on a t-distribution. Otherwise, if data are skewed, distribution-free confidence interval of the median will be calculated. The comparison between before and after blood donation will be conducted by using paired t-test or Wilcoxon signed-rank test, depending on the distribution of data.

9.3.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

All baseline demographic variables collected at enrollment will be summarized using descriptive statistics.

9.3.4 PRIMARY ANALYSIS

The following will cover the planned primary analyses for this study procedure. Unless otherwise specified, statistical analyses will be performed using two-sided hypothesis tests at the overall 5% significance level. No multiple comparison adjustments will be performed.

1. Analysis of measurements taken before and after blood draw

Measurements including RI and individual physiological parameters taken before and after blood draw will be first summarized using descriptive statistics. For each parameter, the absolute and percent differences before and after draw will be calculated and summarized using summary statistics together with 95% confidence interval. The p-value will be calculated using paired t-test or Wilcoxon signed-rank test to compare with zero.

2. Analysis of differences between measurement taken before and after blood draw.

The difference between measurements taken before and after blood draw will be calculated by value before donation minus value after draw for RI and each individual physiological parameter.

10 DATA COLLECTION, RETENTION, AND MONITORING

10.1 DATA COLLECTION

The Investigator will prepare, maintain, and retain complete, current, accurate, organized, and legible Source Documents to record all observations and other pertinent data for each subject. In some instances, case report forms (CRFs) will serve as source documentation. The Investigator or designated study personnel will provide the Sponsor redacted standard procedure records with the subject ID number as applicable. Any required data not collected as standard of care for the blood draw procedure will be captured on study-specific case report forms.

Corrections of data on paper source documents will be made by crossing out the incorrect data and making the GCP-compliant correction. Each correction will be initialed and dated by the study personnel making the correction.

The Investigator is responsible for the information collected on subjects enrolled in the study. All data collected during the study must be reviewed and verified for completeness and accuracy by the Investigator. If any corrections are made after the Investigators signature, the Investigator will also initial and date the correction.

10.1.1 SUBJECT CONFIDENTIALITY

In order to maintain subject confidentiality, records identifying the subject will be kept in a safe and secure location; access to these records will be on a limited basis. Only the subject identification number, gender, and age will identify study subjects on CRFs and other documentation submitted to the Sponsor. A limited number of Sponsor representatives may have access to identifiable information and will take reason able precautions to maintain the confidentiality of the subject's identity.

10.2 DATA RETENTION

All study records will be stored in a safe and secure location. Records will be retained per applicable regulatory requirements, which include for a period of two (2) years after the latter of the following two days: the date which the investigation is terminated or completed, or the date that records are no longer required for purposes of supporting premarket approval applications or a notice of completion of a product development protocol. The Investigator site may transfer custody or records to the Sponsor with appropriate documentation recording the transfer.

10.3 MONITORING

10.3.1 MONITORING PLAN

Monitoring visits will be conducted by representatives of the Sponsor or study site or both according to 21 CFR 812. (c) for non-significant risk device studies and ICH Guidelines. By signing this protocol, the Investigator grants permission to the Sponsor (or designee) and all appropriate regulatory authorities to conduct on-site or electronic monitoring or auditing or both of all appropriate study documentation.

11 STUDY ADMINISTRATION

11.1 AUDITS AND INSPECTIONS

External auditors and government inspectors may evaluate the study and must be allowed access to CRFs, source documents, and other study files. Audit reports will be confidential.

11.2 PROTOCOL AND ICF AMENDMENTS

Sponsor approval is required for any protocol or ICF amendment. Protocol or ICF amendments will not be implemented without prior written IRB approval except as allowed per the IRB procedures/approval and as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided IRBs are notified within five (5) working days. The Informed Consent Form will be reviewed and updated as necessary at the time of the protocol amendment.

11.3 PROTOCOL DEVIATIONS

A protocol deviation is defined as any accidental or unintentional changes to, or non-compliance with the IRB approved research protocol. Any deviation from the protocol must be documented and reported to the Sponsor within ten (10) working days and reported to the IRB as applicable to regulatory requirements. Protocol deviations that pose an immediate risk or significant hazard to subjects must be reported to the Sponsor within 24 hours and reported to the IRB no later than five (5) working days after the emergency occurred. In the instance an Investigator uses a device without obtaining informed consent; the Investigator shall report to the Sponsor and the IRB within five (5) working days as per 21 CFR 812.150 (1) (5).

12 ETHICAL AND OTHER REGULATORY CONSIDERATIONS

It is the responsibility of the Investigator that the study is conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Board (21 CFR 56), and Responsibilities of Clinical Investigators (21 CFR 812 (e)).

12.1 INSTITUTIONAL REVIEW BOARD (IRB) REVIEW

The Protocol, ICF, and any subject facing material (as required) will be reviewed and approved by the IRB prior to study initiation. The Sponsor will maintain responsibility for obtaining IRB approval and submitting all required study reports to the IRB. Amendments to the Protocol, ICF, or any subject facing material will not be implemented without prior written IRB approval unless to eliminate an apparent immediate hazard to subjects. All IRB approvals will be kept in the Trial Master File and Investigator Site File.

12.2 WRITTEN INFORMED CONSENT

The Informed Consent Form (ICF) and Informed Consent process will include all elements required by applicable regulations. Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH, Good Clinical Practice, and US Code of Federal Regulations for Protection of Human Subjects (21 CFR

50.25 [a,b], 21 CFR 50.27, and 21 CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA) when applicable, and local regulations.

A properly executed, written informed consent will be obtained from all subjects prior to entering the subject into the trial, unless waived by the IRB. ICF information will be given in both verbal and written form. The subject must be given an ample amount of time to read the ICF. The subject must provide written consent by signing and dating the approved ICF. A signed copy of the ICF will be provided to the subject; originals will be maintained with the subject's study records.

Assents Forms will not be permitted as subjects must be over the age of 18 to meet the Inclusion/Exclusion criteria. Legally Authorized Representatives will not be permitted as subjects must have the ability to provide written consent to meet the Inclusion/Exclusion criteria.

14 ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 6: Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
BPM	Beats per minute
BP	Blood pressure
C	Celsius
CFR	U.S. Code of Federal Regulations
CM-1500	Zynex Fluid Monitoring System, Model 1500
CRF	Case report form
ECG	Electrocardiogram
e.g.	Exempli Gratia (for example)
F	Fahrenheit
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
lb	Pound; unit of mass
ohms	Plural unit of electrical resistance
mL	Milliliter
mV	Millivolts
PHI	Protected Health Information
PI	Principal Investigator
PPG	Photoplethysmogram
SAE	Serious adverse event
UADE	Unanticipated Adverse Device Event
ZMS	Zynex Monitoring Solutions