CLINICAL PROTOCOL

ZMS-1500-2021-Dialysis

NCT#05125848

11-NOV-2021

CLINICAL PROTOCOL

TITLE	Clinical Evaluation of the CM-1500 During Hemodialysis
PROTOCOL	ZMS-1500-2021-Dialysis
SPONSOR	Zynex Monitoring Solutions (ZMS) 9555 Maroon Circle Englewood, CO 80112
PROTOCOL VERSION	1.0
DOCUMENT REVIEW & APPROVAL	

Sponsor Representative:		
Don Gregg **VP, Zynex Monitoring Solutions**	Signature	Date

Sponsor Representative:		
Laura Seiberlich **Zynex Clinical Affairs**	Signature	Date

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PROTOCOL SIGNATURE PAGE

TITLE	Clinical Evaluation of the CM-1500 during Hemodialysis
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PROTOCOL VERSION	1.0

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): _____

PI Printed Name

_____

PI Signature

_____

Date (DD-MMM-YYYY)

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PROTOCOL AMENDMENT HISTORY

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

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1 INTRODUCTION

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].

The Zynex Monitoring Solutions fluid volume 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, and skin temperature [redacted] When the monitoring session starts, each patient starts with a Relative Index 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.

Hemodialysis is a medical procedure performed to remove fluid and waste products from the blood and to correct electrolyte imbalances. Patients with chronic kidney failure often need to undergo hemodialysis multiple times each week to prevent fluid overload. The environment in which hemodialysis is performed is well-defined, and the amount of fluid volume removed during each session is calculated and recorded. Therefore, examining changes in the RI in hemodialysis procedures will provide valuable insights into the performance of the RI in comparison to the individual parameters that make up the index, as well as the observed changes that may occur in a patient's physical status during a hemodialysis session.

1.1 CLINICAL RATIONALE

The proposed clinical study is designed characterize the changes in the Zynex non-invasive monitoring device (CM-1500) Relative Index to track fluid volume changes in subjects consented to undergo a hemodialysis procedure. An initial feasibility 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, [redacted] Additional research is required to assess Relative Index changes when larger fluid volumes are observed and to determine how the individual parameters impact the overall device performance in a hemodialysis setting.

2 INVESTIGATIONAL PLAN

2.1 OBJECTIVES

The primary objective of the study is to characterize changes in the CM-1500 Relative Index during a hemodialysis procedure.

The secondary objective of the study is to characterize the intersubject and intrasubject variability in Relative Index changes across multiple hemodialysis sessions.

2.2 STUDY DURATION

Enrollment in the study is expected to take up to 3 months, and data analysis may take up to an additional 2 months to complete. Each individual subject's study participation is estimated to last approximately 1-2 weeks but may continue for up to 30 days. If the subject has not completed three (3) monitoring sessions within 30 days, participation will be considered complete, and the subject will be withdrawn from the study.

2.3 STUDY DESIGN

The study is a prospective, single-arm, non-randomized, non-blinded, non-controlled, non-significant risk, single center study enrolling subjects consented to undergo a hemodialysis session as a part of their standard prescribed treatment plan. Subjects will consent to undergo non-invasive monitoring with the CM-1500 during three (3) separate hemodialysis sessions. Attempts will be made to have the monitoring sessions sequentially performed with their subsequently planned hemodialysis sessions. Up to 20 subjects will be consented and enrolled to ensure 15 subjects complete the study with the required number of monitoring sessions.

3 STUDY DEVICE

3.1 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. [redacted] The Relative Index is a unique functionality of the Zynex CM-1500.

3.1.1 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.

3.2 PRINCIPLES OF OPERATION

The CM-1500 measures bioelectrical impedance (ohms), heart rate (BPM), ECG amplitude, 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 [redacted] 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.

3.3 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.

3.4 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 20 adult subjects who meet the inclusion and exclusion criteria will be consecutively enrolled in the study. Subjects who enroll in the study but withdraw before using the device will not be included in the total number of subjects and will be replaced.

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, including connection of the device to the left wrist/hand and maintaining relatively motionless during the session

I.3 18 years of age or older

I.4 Planned to undergo a minimum of three (3) hemodialysis sessions within the two (2) weeks following enrollment.

4.3 SUBJECT EXCLUSION CRITERIA

E.1 Females who are pregnant or breastfeeding

E.2 Undergone an amputation of the left upper extremity

E.3 Subjects with left arm hemodialysis access only

E.4 Diagnosed with dextrocardia

E.5 Subjects who have a pacemaker

E.6 Subjects who have any other underlying condition that would inhibit completion of participation in the study, per Investigator opinion

4.4 SUBJECT WITHDRAW / EARLY TERMINATION

Subjects who withdraw from the study before using the CM-1500 device 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.

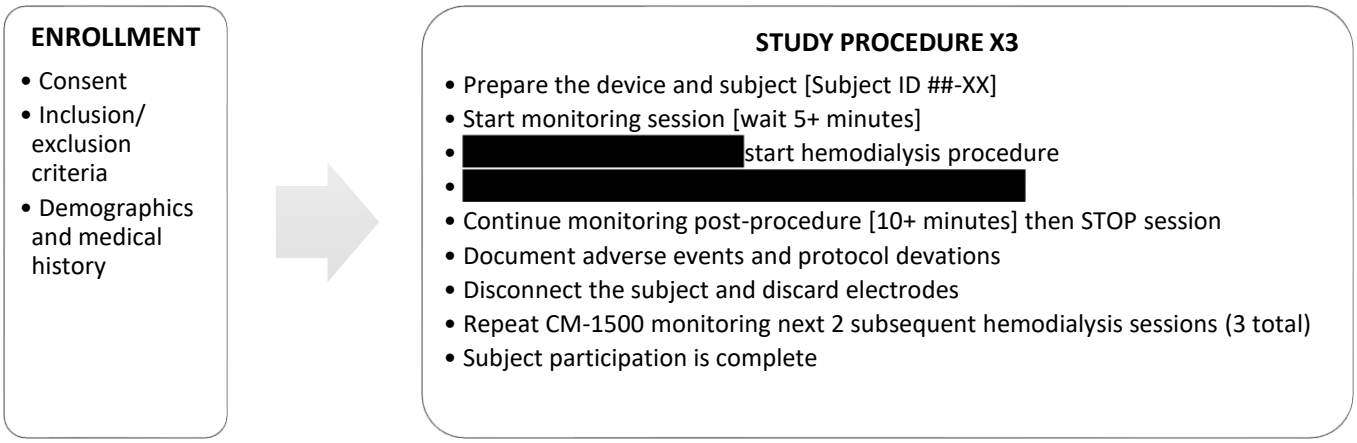
W.2 Subject refuses or is unable to comply with required study procedures.

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 PROCEDURES

Figure 1: Study Procedure Overview



5.1 ENROLLMENT

A subject will be considered enrolled in the study after provided written informed consent.

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.

5.2 BASELINE DATA

Baseline data will include collecting age, biological sex, smoking history, limited medication information, and high-level medical history.

5.3 STUDY PROCEDURE

The study procedure will consist of connecting the CM-1500 to the study subject on their left arm/wrist and starting a monitoring session at least 5 minutes prior to starting the scheduled hemodialysis procedure, wearing the monitor during the hemodialysis session, and continuing to wear the monitor for 10 minutes after the procedure is complete. The Investigator's standard post-treatment hemodialysis record will be collected containing the prescription information, machine set-up, vitals, pre- and post-treatment data collection and assessment, medications administered, and intradialytics.

5.3.1 PREPARING DEVICE FOR OPERATION

The Investigator or qualified designated study personnel will prepare the device for use by referencing the Instructions for Use (IFU) manual following the study-specific steps outlined below.

S1. Complete the Unpacking, Inspection, and Accountability procedures and associated forms (refer to IFU for the full procedure).
S2. Ensure the device is in a secure and stable location (refer to IFU for full procedure).
S3. Connect the power supply cord to the display monitor and to an electrical outlet. The light will illuminate on the power adapter when it is connected to power.
S4. Connect the CM-1500 wrist cuff trunk cable to the display monitor. The cable should double-click into the correct insertion position.
S5. Connect the CM-1500 wrist cuff to the trunk cable. The cable should double-click into the correct insertion position.
S6. Power on the device by pressing the external "ON/OFF" button located on the right side of the display monitor.
S7. Press the "SETUP" button and select the desired user preferences, subject information (subject number), data storage mode, and device information. Press "SAVE" after all desired setup options are selected—the device will return to the Monitoring Screen.

a. Select male/female
b. Ensure the date/time of the CM-1500 aligns with the times that will be recorded in the post-treatment hemodialysis record from the hemodialysis machine and clinician watches
c. **Enter the subject ID as subject number (01-20) followed by AA, BB, or CC corresponding to session 1 (AA), 2 (BB), or 3 (CC).** For example, the first subject, first session subject ID will be 01-AA and the next session will be 01-BB.

S8. Insert a USB external storage drive (refer to "Data Storage Mode" in the IFU). The USB external storage drive should be labeled externally with the device serial number. The USB indicator icon should appear on the Monitoring Screen, signaling that the USB storage drive is connected and recognized.

5.3.2 PREPARING THE SUBJECT FOR DEVICE OPERATION

After the device is prepared for operation, the Investigator or qualified designated study personnel will prepare the subject for device operation by referencing the Instructions for Use (IFU) manual and following the steps outlined below. The subject will be placed in a supine or sitting position after the device is prepared for operation and maintain this position through observation.

S9. Clean the subject's skin on his or her left wrist.
S10. Take the small white connector/electrode array and remove the transparent plastic film attached to the electrodes to expose the adhesive. Place the small white connector/electrode array on the dorsal (top) of the subject's left wrist. The white connector shall be pointed medially (inward) towards the subject's body.
S11. Take the large blue connector/electrode array and remove the transparent plastic film attached to the electrode to expose the adhesive. Place the large blue connector/electrode array on the left side of the neck's base and down across the front of the shoulder (above the clavicle). The blue connector shall point away from the neck, extending toward the direction of the left shoulder.
S12. Place the wrist cuff on the subject's left wrist (above or over the top of the white electrode array), with the trunk cable connection pointing up the arm, and secure the wrist strap around the left wrist. The cuff should be snug with no gap between the wrist cuff and skin. The wrist cuff should not be able to slide or rotate on the wrist nor should it be too tight or restricting of blood flow.
S13. Place the PPG finger glove on the subject's left digitus II manus (Index) fingertip. The white cable/top side of the finger glove should be on the dorsal (top) side of the finger. The fingertip shall be touching the end of the inside of the glove. Fingernails will often protrude through the end of the finger glove, which is normal.
S14. Examine the trunk cable to ensure that it is connected securely to the CM-1500 display monitor and the wrist cuff.

S15. Connect both CM-1500 electrode array sets to the corresponding electrode lead cables protruding from the wrist cuff. The blue connector/electrode array set shall connect to the blue lead cable connector on the wrist cuff. The white connector/electrode array shall connect to the white lead cable connector on the wrist cuff. The lead cable connectors are shaped to match the electrode connectors- ensure connectors are properly aligned before inserting (DO NOT FORCE THE CONNECTION).

5.3.3 CM-1500 MONITORING SESSION

The Investigator or designated study personnel will operate the device by referencing the Instructions for Use (IFU) manual and following the study-specific steps outlined below.

S16. Start the monitoring session by pressing "START" on the CM-1500 display monitor/monitoring screen. A message will appear informing the user that the monitoring session is in progress and the patient's baseline is being established. The device will begin to measure all five (5) parameters.

S17. As monitoring continues, the display will show ECG and PPG pulse waveforms along with the Relative Index graph over time. Baseline measurements, for all parameters, are taken at the beginning of the monitoring session [redacted]. The subject should be relaxed during baseline establishment. The subject should remain in a supine or sitting position. The baseline measurement will continue for a minimum of 5 minutes. [redacted]

S19. Continue the monitoring session during the hemodialysis session. **Upon completion of the session,** [redacted] **continue the monitoring for a minimum of ten (10) minutes.** [redacted] **If the subject needs to move to a different location during the 10-minute post-hemodialysis monitoring period, the time of movement should be noted on the CRF.**

S20. After the observation period has passed, "STOP" shall be pressed to end the monitoring session. The user will need to press "Yes" on the confirmation window to stop the monitoring session after pressing "STOP".

S21. Document any observations or adverse events that occur throughout the entirety of the monitoring session.

S22. After the monitoring session is stopped, remove the electrode array sets from the subject and dispose of the electrodes and wrist strap per site guidelines. Wipe down wrist cuff and cables per the IFU for next subject use.

5.4 REPEAT STUDY PROCEDURES AND STUDY COMPLETION

Subjects will continue to be monitored at each of their next two (2) subsequent hemodialysis sessions. If the device is not available or the subject is unable to complete the monitoring session at the following hemodialysis session, the next available hemodialysis session will be acceptable, and the date of the last procedure and number of hemodialysis sessions in between monitoring sessions will be captured on the case report form. All attempts should be made to complete the subject's participation in the study within two (2) weeks of enrollment.

For the remaining two monitoring sessions, the procedure will continue the same as previously performed. After the third CM-1500 monitoring session is complete, the subject's participation in the study is considered complete. If the subject elects to withdraw from the study before completing their third monitoring session, or if 30 days have passed since the initial monitoring session, subject withdrawal will be captured on the case report form. Additional subjects will be enrolled (up to 20) until 15 complete data sets of three (3) monitoring sessions each have been complete.

5.5 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.

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. 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 device shall be cleaned before each use. Cleaning procedures will be followed per the Instructions for Use (IFU) manual and institutional procedures. The device should always be turned off

and disconnected before cleaning. The study device and any unused accessories shall be returned to the Sponsor after study completion.

7 RISKS & BENEFITS

7.1 RISK DETERMINTATION & REDUCTION

This study is determined to be exempt and 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 hemodialysis procedure. The study device and use of the device do 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 or discomfort could occur from the electrodes
- [Possible, Mild] Discomfort could occur due to lying in a supine position for duration of the hemodialysis 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 performing hemodialysis 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 hemodialysis procedure or study procedure, and outcome. These definitions are in the corresponding tables below. All adverse events related to the hemodialysis 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 Hemodialysis or Study Procedure

Relationship	Description
None	Causal relationship can be ruled out
Possible – Hemodialysis Procedure	Causal relationship is reasonably possible to the hemodialysis procedure (i.e., the relationship cannot be ruled out)
Possible – Study Procedure/Device	Causal relationship is reasonably possible to the protocol-required study procedure and/or device (i.e., the relationship cannot be ruled out)
Yes – Hemodialysis Procedure	Causal relationship to the hemodialysis procedure is certain
Yes – Study Procedure/Device	Causal relationship to the study procedure and/or 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 hemodialysis 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 and to the reviewing IRB 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
Principal Investigator	Jonathan Tolins, MD InterMed consultants 6600 France Ave S, Suite 162 Edina, MN 55435 [redacted]
Sponsor Representative	Zynex Monitoring Solutions E: Clinical@zynex.com [redacted]
IRB	WCG IRB 1019 39th Ave., SE, Suite 120 Puyallup, WA 9837 [redacted]
Mailing Address	Zynex Monitoring Solutions Attn: ZMS Clinical 9555 Maroon Circle Englewood, CO 80112

9 STATISTICAL METHODS AND CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

This is a hypothesis generating study; therefore, hypothesis testing will not be performed. The sample size of 15 subjects is empirically determined to be sufficient for an early-phase pilot study characterizing the performance of the Relative Index during a hemodialysis procedure. The results of the study will be used to help the Sponsor determine if an appropriately powered clinical study can be defined.

9.2 ANALYSIS SET

All eligible subjects who were enrolled in the study and used the study device will be included in the analyses. Subjects who withdraw after enrollment and before device use will be excluded from the analyses.

9.3 DESCIPTIVE STATISTICS

Descriptive statistics will be calculated for all objectives and measures. Continuous variables will be summarized in terms of the mean, standard deviation (SD), median, quartiles, minimum, maximum and number of observations. Categorical variables will be summarized in terms of the number of subjects providing data, frequency count and percentage.

9.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

9.5 STATISTICAL ANALYSIS

The data for this study will be summarized using descriptive statistics. There is no formal hypothesis testing planned. Point estimates and the corresponding confidence intervals will be presented for the statistical analysis.

The primary evaluations pertaining to the performance of the CM-1500 device will examine the behavior the Relative Index value in accordance with subject outcomes and conditions that present during the hemodialysis sessions. Baseline performance of the CM-1500 device will be set in the Relative Index before the hemodialysis sessions. The primary analysis will utilize the descriptive statistics to characterize the changes in the CM-1500 Relative Index during the hemodialysis sessions, comparing to the baseline values. The analysis, however, can include investigation into individual vital sign parameters that the CM-1500 device (or another source) produces during a subject's session or 10-minute post-dialysis observation period.

The average of the Relative Index at baseline and each following hemodialysis sessions will be calculated first for the variability analysis. The inter-subject (between subject) and intra-subject (within-subject) variability in the Relative Index changes across multiple hemodialysis sessions will be estimated using the variance component analysis through a random effects model that includes only subject and hemodialysis session as random effects. The variance and % coefficient of variation (%CV) will be computed for the components of between-subject and within-subject through the model.

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 post-treatment forms with the corresponding subject ID number for each of the hemodialysis procedures. Any required data not collected as standard of care for the hemodialysis procedure will be captured on study-specific paper case report forms.

Corrections of data on paper CRFs or source documents will be made by crossing out the incorrect data and making the 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 reasonable 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 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 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 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 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 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.

[redacted]

13 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	Cardiac Monitor, Model 1500
CRF	Case report form
ECG	Electrocardiogram
e.g.	Exempli Gratia (for example)
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
PHI	Protected Health Information
PI	Principal Investigator
PPG	Photoplethysmogram
SAE	Serious adverse event
UADE	Unanticipated Adverse Device Event
ZMS	Zynex Monitoring Solutions