# CLINICAL PROTOCOL

**ZMS-1500-2001**

**NCT#04706221**

**13-MAY-2021**

# CLINICAL PROTOCOL

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|---|---|
| **TITLE** | Clinical Evaluation of the CM-1500 in Postoperative Abdominal and Pelvic Surgery Patients |
| **PROTOCOL NO.** | ZMS-1500-2001 |
| **SPONSOR** | Zynex Monitoring Solutions (ZMS)<br>9555 Maroon Circle<br>Englewood, CO 80112 |
| **IRB/ETHICS COMMITTEE** | Wake Forest University Health Sciences<br>Office of Research Institutional Review Board<br>Medical Center Boulevard<br>Winston-Salem, NC 27157-1023 |
| **PROTOCOL VERSION** | 01/03/2021 |
| **IDE:** | NA |
| **DOCUMENT REVIEW & APPROVAL** | |

| | | | |
|---|---|---|---|
| **Investigator(s):** | Ashish Khanna, MD | Signature | Date |
| **Sponsor Representative(s):** | | Signature | Date |

## CONFIDENTIALITY STATEMENT

## PROTOCOL SIGNATURE PAGE

| | |
|---|---|
| **TITLE** | Clinical Evaluation of the CM-1500 in Postoperative Abdominal and Pelvic Surgery Patients |
| **PROTOCOL NO.** | ZMS-1500-2001 |
| **SPONSOR** | Zynex Monitoring Solutions (ZMS)<br>9555 Maroon Circle<br>Englewood, CO 80112 |
| **IRB APPROVAL DATE** | 12-JAN-2021 |
| **PROTOCOL VERSION** | 1.1 |

The signature below constitutes I have read, understood, and 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 IRB; 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):** Ashish Khanna, MD

PI Printed Name

PI Signature

Date (DD-MMM-YYYY)

## CONFIDENTIALITY STATEMENT

## PROTOCOL AMENDMENT HISTORY

| Version Number | IRB Approval Date | Description of Change(s) |
|---|---|---|
| 1.0 | 12-JAN-2021 | Initial protocol; no changes |
| 1.1 | 13-MAY-2021 | Increased the number of subjects from 100 to 200 and removed laparoscopic so that both open and laparoscopic procedures are allowed to be enrolled. |

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## CONFIDENTIALITY STATEMENT

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# 1 ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definition of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| BPM | Beats per minute |
| C | Celsius |
| CFR | U.S. Code of Federal Regulations |
| CM-1500 | Cardiac Monitor, Model 1500 |
| CRF | Case report form |
| EC | Ethics Committee |
| ECG / EKG | Electrocardiogram |
| e.g. | Exempli Gratia (for example) |
| eCRF | Electronic Case Report Form |
| 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 Harmonisation |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| ISO | International Organization for Standardization |
| lb. | Pound; unit of mass |
| ohms | Unit of electrical resistance, plural |
| OTC | Over-the-counter |
| mL | Milliliter |
| MRI | Magnetic Resonance Imaging |
| PACU | Post-anesthesia Care Unit |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PPG | Photoplethysmogram |
| SAE | Serious adverse event |
| SOP | Standard Operating Procedure |
| Sub-I | Sub-Investigator |
| UADE | Unanticipated Adverse Device Event |
| ZMS | Zynex Monitoring Solutions |

## 2 INTRODUCTION

Postoperative hemorrhage incidence can vary depending on the type of surgery, but it can lead to severe clinical complications ranging from mild anemia to fatal hemorrhagic shock. One study conducted by Mañas-Gómez et al. (2011) evaluated 107 post-pancreaticoduodenectomy (PD) patients between January 2005 and December 2008 and found that 16.82% (18/107) patients hemorrhaged after PD. Of those, four (4) of the eighteen (18) patients hemorrhaged early (< 24 hours).[1] The study also found that hemorrhage after pancreatic resection may be considered a complication with a high mortality rate. Ansari et al. (2016) conducted a retrospective observational study on 500 consecutive patients undergoing major pancreatic resections.[2] The study found that 13.6% (68 patients) developed post-pancreatectomy hemorrhage.[2]

Monitoring and detecting these fluid changes postoperatively can be complicated, and standard operating procedures vary. The Cardiac Monitor, Model 1500 (CM-1500), uses a personalized approach by non-invasively and simultaneously monitoring five (5) physiological parameters, including bioelectrical impedance, ECG Amplitude, PPG Amplitude, heart rate, and skin temperature. [redacted] When the monitoring session starts, each patient starts with a Relative Index of 100 signifying parameters near their original baseline value. The Relative Index value acts as a combinational score [redacted]

## 3 INVESTIGATIONAL PLAN

### 3.1 OBJECTIVE

The primary objective is to evaluate the changes in the Relative Index in post abdominal or pelvic surgery patients (both laparoscopic and open procedures).

### 3.2 STUDY DURATION

Enrollment is expected to take up to 12 months. Data analysis is expected to take up to 6 months after enrollment is completed.

### 3.3 STUDY DESIGN

The study is a prospective, single-arm, non-randomized, non-controlled, single-center study enrolling adult subjects.

## 4 CM-1500 (“DEVICE”)

### 4.1 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.

### 4.1.1 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.

## 4.2 PRINCIPLES OF OPERATION

The CM-1500 measures bioelectrical impedance (ohms), heart rate (BPM), ECG amplitude, PPG amplitude, and skin temperature (°C). As parameters change, towards indications of fluid change/imbalance, the Relative Index, [redacted], will compound these changes into a singular value [redacted]
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.

## 4.3 INDICATIONS FOR USE

Per the device's FDA clearance, the indications for use including monitoring of the following parameters and their relative changes, indicative of relative changes in fluid volume in adult patients: bioelectrical impedance, heart rate, ECG amplitude, and PPG amplitude.

## 4.4 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.

## 5 SUBJECT POPULATION AND SELECTION

### 5.1 POPULATION AND ANTICIPATED NUMBER OF SUBJECTS

We anticipate up to 200 adult subjects who meet the inclusion and exclusion criteria to enroll in the study.

### 5.2 SUBJECT INCLUSION CRITERIA

I.1 Ability to provide written informed consent
I.2 Ability and willingness to comply with study procedures and duration requirements
I.3 18 years of age or older
I.4 Undergoing an abdominal or pelvic surgery within the next 10 days, be it laparoscopic or open procedure

### 5.3 SUBJECT EXCLUSION CRITERIA

E.1 Females who are pregnant or breastfeeding
E.2 Participation in other clinical studies involving experimental drugs or devices
E.3 Undergone an amputation of the left upper extremity
E.4 Diagnosed with Dextrocardia
E.5 Subjects who have a Pacemaker

### 5.4 SUBJECT SCREEN FAIL CRITERIA

Subjects who are determined to be a Screen Fail may be replaced.

SF.1 After Enrollment, the subject is found not to meet the inclusion/exclusion criteria. Enrollment is defined as the subject has provided verbal Informed Consent.

### 5.5 SUBJECT WITHDRAW / EARLY TERMINATION CRITERIA

Subjects who are withdrawn from the study before using the device may be replaced. Subject withdrawal/early termination criteria are listed below.

W.1 The subject requests to be withdrawn from the study or withdraws consent.
W.2 The subject refuses to comply with the required study procedures.
W.3 An Adverse Event (AE) (related to the investigation or not) 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.
W.5 The Sponsor terminates the Investigator, Site, or the Study.

### 5.6 CONCOMITANT MEDICATIONS/ CONCURRENT MEDICATIONS

All concomitant medications will be recorded from screening through study completion.

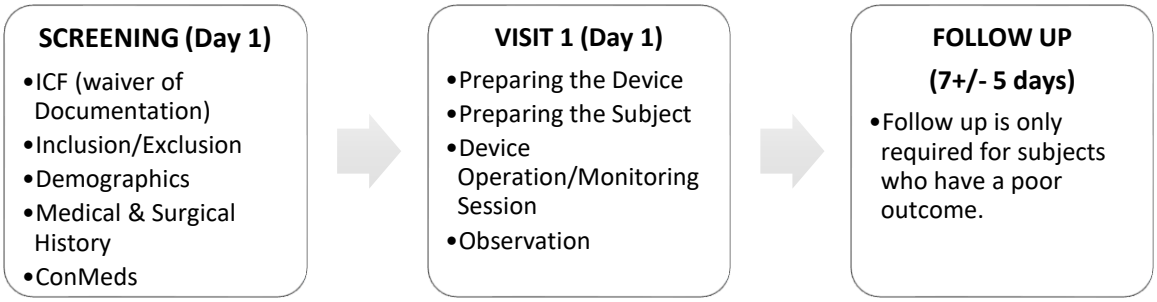
#### 5.6.1 PROHIBITED MEDICATIONS

Prohibited medications include any experimental drugs while participating in the study (E.2).

## 6 STUDY GROUPS & ASSIGNMENT

This study is a prospective, non-randomized, non-controlled study. Each subject will undergo the same procedures.

## 7 STUDY PROCEDURES




### 7.1 ENROLLMENT

A subject has enrolled in the study after the subject has provided written informed consent.

#### 7.1.1 INFORMED CONSENT/ RESEARCH INFORMATION SHEET

All potentially eligible subjects will undergo formal screening by members of the research teams at each site and confirmed by the site Investigator to be a candidate for the study. The PI or his designee will review and explain the contents of the informed consent document to the eligible subject. The potential subject or family member will be informed of the purpose of the study, the randomization procedure, and the risks and benefits of participation. The potential subject will also be informed that he/she may refuse to participate, and that even if he/she consents to participate he/she may withdraw from the study at any time.

If the subject does not consent to participate, he/she will not be admitted to the study.

#### 7.1.2 SCREENING

Screening procedures are estimated to take approximately 1 hour. Screening procedures include obtaining demographics, medical and surgical history, and concomitant

medications. This information is gathered via chart review and may be self-reported by the subject.

### 7.1.3 DEMOGRAPHICS

Demographic information, including the subject's year of birth or age, sex, gender, race, and ethnicity, will be recorded at Screening.

### 7.1.4 MEDICAL & SURGICAL HISTORY

Relevant medical and surgical history will be recorded at the Screening. This includes any medical condition(s) diagnosed or surgeries that occurred before Screening through study completion. The height (inches), weight (pounds), and the type of surgery the subject is undergoing will also be recorded.

### 7.1.5 CONCOMITANT MEDICATIONS

Concomitant Medications (conmeds) are defined as prescription, over-the-counter OTC drugs, or dietary supplements a subject takes while participating in the study and 2 weeks prior. All concomitant medications will be recorded at Screening through study completion.

## 7.2 VISIT 1

Visit 1 is estimated to take approximately 2-6 hours. Visit 1 includes preparing the device for use, preparing the subject for device use, operating the device (monitoring session), and observation. Visit 1 will occur on the same day as Screening.

### 7.2.1 PREPARING DEVICE FOR USE

The Investigator or qualified designated study personnel will prepare the device for use by referencing the Instructions for Use (IFU) manual and 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 the full procedure).
S3. To supply power to the CM-1500, connect the power supply cord to the display monitor and an electrical outlet. The light will illuminate on the power adapter when it is connected to power.
S4. To connect the display monitor to the wrist cuff, 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, patient information, device storage mode, and device information. Press "SAVE" after all desired setup options are selected.

   a. On the "SETUP" screen, complete user preferences, subject information (sex and subject number), data storage mode, and review device information. By pressing "SAVE," the device will return to the Monitoring Screen.

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 subject number. The USB should display a solid red light.

### 7.2.2 PREPARING THE SUBJECT FOR DEVICE USE

After the device is prepared for use, the Investigator or qualified designated study personnel will prepare the subject for device use by referencing the Instructions for Use (IFU) manual and following the study-specific steps outlined below. The subject's position (supine, prone, fowlers, R/L lateral recumbent) throughout the study may be recorded. The subject will be prepared for device use within 15 minutes (but no longer than 1 hour) after the subject's surgery. Monitoring/device use will occur in the recovery room and PACU.

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 point 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 slide or rotate without being too tight or restricting 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 from 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.

> **NOTE**: Ensure connectors are properly aligned before inserting (DO NOT FORCE THE CONNECTION).

### 7.2.3 DEVICE USE/OPERATION

The Investigator or qualified designated study personnel will operate the device by referencing the Instructions for Use (IFU) manual and following the study-specific steps outlined below. Device operation will begin within 15 minutes (but no longer than 1 hour) after the subject's surgery. Sites will not use the device for clinical decisions but instead follow their standard operating procedures for monitoring postoperative subjects.

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. 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. [redacted] The subject should remain in a supine position (with an allowance to be 30 degrees head up) if possible.

S18. Continue the monitoring session for at least 60 minutes but no longer than 6 hours postoperatively. The device will monitor until "STOP" is pressed on the monitoring screen. Document any observations or adverse events that occur during the monitoring session.

S19. After the monitoring session is stopped, remove the electrode array sets from the subject and dispose of the electrodes per site guidelines.

### 7.2.4 OBSERVATION

The site will follow its standard operating procedure (SOP) to monitor postoperative subjects in the recovery room and PACU. The Investigator or qualified designated study personnel will continue monitoring the subject and observe the subject for at least 1 hour but no longer than 6 hours postoperatively. Any observations can be recorded (by using the mark event button on the CM-1500 device), but it is not required as all relevant events will be recorded in the patients medical records as per the SOP of the site. Observations may include but are not limited to indoor temperature of the postoperative recovery room or PACU, time and type of medication delivery, vital sign data (as obtained as part of the sites SOP), and the subject's position. Following/using the site's SOP, should the subject show signs of hemorrhage or a potentially poor outcome,the site will note this in the EMRs including time and date of the observation.

After the observation period is complete, the monitoring session will be stopped, and the electrode array sets will be removed and disposed of. Redacted medical records will be provided to the Sponsor.

## 7.3 UNANTICIPATED DEVICE EFFECT (UADE)

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

## 7.4 FOLLOW-UP VISIT/CONTACT

In the event of a poor outcome due to the subject's surgery, the Investigator or qualified designated study personnel will perform follow-up contact via telephone call 7(±5) days after the outcome occurred. The Investigator or study personal will record any follow-up attempts or contact made. Should the outcome not be resolved in 7(±5) days, follow up might continue until resolved, or the outcome will be notated as unknown upon approval by the Sponsor.

## 7.5 SUBJECT COMPLETION

A subject has completed the study when all Screening, Visit 1, and, when applicable, follow-up contact is completed and documented.

## 7.6 SCHEDULE OF EVENTS TABLE

Table 2: Schedule of Events

| STUDY PROCEDURE | SCREENING Day 1 | VISIT 1 Day 1 | FOLLOW UP CONTACT Day 7 (± 5) |
|---|---|---|---|
| Informed Consent (waiver of documentation) | X | | |
| Inclusion/Exclusion | X | | |
| Demographics | X | | |
| Medical and Surgical History | X | | |
| Concomitant Medications | X | | (X) if applicable |
| Prepare Device for Use | | X | |
| Prepare Subject for Device Use | | X | |
| Device Operation/Monitoring Session | | X | |
| Observation | | X | |
| Adverse Events Review | | X | (X) if applicable |
| Follow-Up Contact | | | (X) if applicable |

# 8 STUDY SUPPLIES AND EQUIPMENT

## 8.1 STUDY SUPPLIES

Study-specific supplies will include alcohol wipes for CM-1500 electrode application(s).

## 8.2 DEVICE EQUIPMENT

CM-1500, including the display monitor and all component accessories.

## 8.3 SAFETY EQUIPMENT

No additional study-specific safety equipment will be required for the investigation. The site will follow their postoperative standard operating procedures.

# 9 DEVICE MANAGEMENT

## 9.1 UNPACKING AND INSPECTION

It is the responsibility of the Principal Investigator (PI) to ensure that all devices are unpacked and inspected prior to using in any study procedures. Upon arrival, the Investigator will remove the device display monitor and accessories from the shipping container; ensure all device components are received; complete the unpacking and inspection checklist in Appendix A. 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.

## 9.2 ACCOUNTABILITY

It is the responsibility of the Principal Investigator to ensure all devices are inventoried and accounted for. The Investigator or qualified designated study personnel will record

all information on the Device Accountability logs (Appendix B) and maintain a copy in the Investigator Site Files (ISF).

### 9.3 STORAGE

The device(s) will be stored at the study center. When not in use, the device(s) 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.

### 9.4 DISPENSATION

The device shall only be used under the supervision of the Principal Investigator. Study Personnel shall not use the device on any person not authorized to receive it.

### 9.5 LABELING

Investigational device(s) will be labeled with the name and place of business of the manufacturer, quantity of contents if applicable, and the statement "CAUTION-Investigational Device. Limited by Federal (U.S.) Law to Investigational Use." In the instance that a production (commercial) device is used, investigational labels will not be applicable, and instead, production labeling will be used.

### 9.6 CLEANING

The device shall be cleaned before each use. Cleaning procedures will be followed per the Instructions for Use (IFU) manual. The device should always be turned off and disconnected before cleaning. The site will follow site-specific COVID19-related cleaning policies as applicable.

### 9.7 RETURN

The device(s) shall be returned to the Sponsor after study completion.

## 10 RISKS & BENEFITS

### 10.1 RISK DETERMINATION

This investigation is a Piovotal study that is determined to be an non-exempt, non-significant risk investigation. An Investigational Device Exemption (IDE) will be submitted based on this determination. The device will be used as intended and no clinical decisions will be made based off of the information obtained.

### 10.2 RISKS

The CM-1500 is a Class II, non-invasive, non-significant risk medical device and does not meet the definition of significant risk under 21 CFR 812.3(m). Adverse events related to the investigation will be recorded and analyzed to evaluate their significance. A report will be written on the findings. There may be other risks that are unknown.

10.2.1 RISKS: USING THE DEVICE

- [Possible, Rare] Skin irritation could occur from the electrodes

10.2.2 WARNINGS: CM-1500 DEVICE

- When using the external power supply, this electrical device does not incorporate a power switch to isolate the system from the ac mains. Unplug the power cord of the ac adapter from the ac mains outlet in order to completely disconnect from the main ac power. Ensure that the AC outlet used for the CM-1500 is easily accessible.
- **BURN HAZARD**: Simultaneous connection of a patient to high-frequency surgical equipment or electrocautery may result in burns at the site of the electrodes and possible damage to the CM-1500.
- **BURN HAZARD**: Do not use the CM-1500 or sensors during magnetic resonance (MR) scanning. The induced current could potentially cause burns. The CM-1500 may affect the MR device, and the MR device may affect the accuracy of the CM-1500 parameters and measurements.
- **BURN HAZARD**: Do not use the CM-1500 or sensors during defibrillation.
- **EXPLOSION HAZARD**: Do not use the CM-1500 in the presence of flammable anesthetics or other flammable substances in combination with air, oxygen-enriched environments, or nitrous oxide.
- **ELECTRIC-SHOCK HAZARD**: Do not open the CM-1500 cover. Only a qualified operator may perform maintenance procedures specifically described in the IFU manual. Refer to Zynex for the repair of this equipment.
- **ELECTRIC-SHOCK HAZARD**: Do not open the power adapter. Refer to Zynex for the repair or replacement of this equipment. **ONLY USE AN APPROVED POWER SUPPLY THAT SATISFIES THE Power Supply Specifications!**
- To protect against injury from electric shock, follow these guidelines:
    - Avoid placing the device on surfaces with visible liquid spills.
    - Do not soak or immerse the device in liquids.
    - Use cleanings solution sparingly and only externally on the device

10.2.3 CAUTIONS: CM-1500 DEVICE

- Tissue damage can be caused by an incorrect application or use of a sensor (e.g., fastening the wrist cuff too tightly). Inspect the sensor sites as directed to ensure skin integrity, correct positioning, and adequate adhesion of the sensors and electrodes.
- Do not apply sensors (including electrodes) to broken or damaged skin.
- Do not autoclave, pressure sterilize, or gas sterilize the CM-1500.

- Do not soak or immerse the monitor in any liquid.
- Use the cleaning solution, sparingly. The excessive solution can flow into the monitor and cause damage to internal components.
- Do not touch, press, or rub the display panels with abrasive cleaning compounds, instruments, brushes, rough surface materials, or bring them into contact with anything that could scratch the panel.
- Do not use petroleum-based or acetone solutions or other harsh solvents to clean the CM-1500. These substances degrade the instrument's materials, and instrument failure may result.
- Do not use damaged sensors and electrodes. Do not use a sensor with exposed optical or electrical components.
- Do not immerse sensors in water, solvents, or cleaning solutions (the sensors and connectors are not waterproof). Do not sterilize by irradiation, steam, autoclave, or ethylene oxide.
- Do not use damaged electrode or trunk cables.
- Do not immerse cables in water, solvents, or cleaning solutions. The patient cable connectors are not waterproof. Do not sterilize by irradiation, steam, autoclave, or ethylene oxide.
- Do not attempt to reprocess, recondition, or recycle Zynex sensors, electrodes, wrist straps, or cables as these processes may damage the components, potentially leading to patient harm.

10.2.4 CONTRADICTIONS: CM-1500 DEVICE

- The CM-1500 is contraindicated for use as an apnea monitor.
- The CM-1500 is contraindicated for patients who have undergone amputation of the left upper extremity.
- The CM-1500 is contraindicated for pregnant patients and children.
- The CM-1500 is contraindicated for use in the Magnetic Resonance Imaging (MRI) environment.
- The CM-1500 is contraindicated for Dextrocardia.

10.3 REDUCING RISKS TO A MINIMUM

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

### 10.4 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.

## 11 SAFETY ASSESSMENT AND MANAGEMENT

### 11.1 SAFETY PARAMETERS

Safety will be assessed by summarizing adverse events.

### 11.2 MEDICAL DEVICE REPORTING

The Sponsor will follow internal Standard Operating Procedures.

### 11.3 SAFETY DEFINITIONS

#### 11.3.1 ADVERSE EVENT (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence, whether or not related to the device or investigational procedure(s). AE's are characterized by grading, actions taken, relationship to the investigation, and outcome. These definitions are defined in the corresponding tables below.

Table 3: 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 |

Table 4: Adverse Events Action(s) Taken

| Action Taken | Description |
|---|---|
| None | No actions were taken |
| Medications | Subject required medication(s) |
| Other Treatment Required | Subject required other treatment(s) |
| Discontinued Study | Subject was discontinued from the study |

Table 5: Adverse Event Relationship to Investigation

| Relationship | Description |
|---|---|
| None | Causal relationship can be ruled out |
| Possible | Causal relationship is reasonably possible (i.e., the relationship cannot be ruled out) |
| Definitely | Causal relationship is certain |

Table 6: Adverse Event Outcome

| Outcome | Description |
|---|---|
| Death | Death was an outcome of the adverse event. |

| | |
|---|---|
| Life-Threatening | Substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the subject. * |
| Hospitalization (initial or prolonged) | Admission to the hospital or prolongation of hospitalization as a result of the adverse event. ** |
| Disability or Permanent Damage | The adverse event resulted in a substantial disruption of a subject's normal ability to conduct normal life functions. |
| Congenital Anomaly/Birth Defects | Exposure to a medical product prior to conception or during pregnancy resulting in an adverse outcome in the child. |
| Other Serious or Important Medical Events | Checked if the event does not meet other outcomes, but the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes. |
| Required Intervention to Prevent Permanent Impairment/damage | The medical or surgical intervention was necessary to preclude permanent impairment of body function or prevent permanent damage to a body structure, either situation to be due to the use of a medical product. |

### 11.3.2 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. AE's severity grading, action(s) taken, relationship to the investigation, and the outcome will all be used for SAE's.

*Whereas 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 the event was more severe.

**Whereas 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.

### 11.3.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An unanticipated adverse service 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.

Table 7: Unanticipated Adverse Device Effect Subject Outcome

| Outcome (check all that apply) | Description |
|---|---|

| | |
|---|---|
| Death | Death was an outcome of the adverse device effect. |
| Life-Threatening | Substantial risk of dying at the time of the adverse device effect or use or continued use of the device might have resulted in the death of the subject. * |
| Hospitalization (initial or prolonged) | Admission to the hospital or prolongation of hospitalization as a result of the adverse device effect. ** |
| Disability or Permanent Damage | The adverse device effect resulted in a substantial disruption of a person's normal ability to conduct normal life functions. |
| Congenital Anomaly/Birth defects | Exposure to a medical product prior to conception or during pregnancy resulting in an adverse outcome in the child. |
| Other Serious or Important Medical Events | Checked if adverse device effect does not meet other outcomes, but the effect may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes. |
| Required Intervention to Prevent Permanent Impairment/damage | The medical or surgical intervention was necessary to preclude permanent impairment of body function or prevent permanent damage to a body structure, either situation to be due to the use of the device. |

*Whereas 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 the event was more severe.

**Whereas 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.

Table 8: Unanticipated Adverse Device Effect

| Device Effect | Description |
|---|---|
| Death | The device effect resulted in the death of a subject |
| Serious Injury | The device effect resulted in Serious Injury to the subject |
| Malfunction | The device effect resulted in a malfunction |

## 11.4 RECORDS

Records of events will be recorded in the source document and Case Report Form (CRF). In the instance a CRF is used as a source document, it will only be reported in the CRF.

## 11.5 SAFETY REPORTING

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

Investigators shall submit to the Sponsor and to the reviewing IRB 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 ten (10) working days after the Investigator learns of the effect. Sponsors will evaluate UADE's.

### 11.5.1 REPORTING EVENTS & SAFETY CONTACTS

Events will be reported, in writing, to the Principal Investigator, Sponsor, and IRB 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.

Table 9. Safety Reporting Contacts

| Contact | Contact Information |
|---|---|
| Principal Investigator | Ashish Khanna, MD, FCCP, FCCM<br>Wake Forest School of Medicine, Associate Professor<br>[redacted] |
| Sponsor Representative | Zynex Monitoring Solutions<br>E: Clinical@zynex.com<br>[redacted] |
| Institutional Review Board | Wake Forest University Health Sciences<br>Office of Research Institutional Review Board<br>Medical Center Boulevard<br>Winston-Salem, NC 27157-1023<br>[redacted] |
| Mailing Address | Zynex Medical<br>Att: ZMS Clinical<br>9555 Maroon Circle<br>Englewood, CO 80112 |

## 12 STATISTICAL METHODS AND CONSIDERATIONS

### 12.1 SAMPLE SIZE DETERMINATION

The sample size of up to 200 subjects was determined feasible.

### 12.2 DATA SETS ANALYZED

All eligible subjects who completed Screening and used the device will be included in the analysis. Subjects who withdraw after Screening and before device use will be excluded.

### 12.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following will be summarized: age, sex, race, ethnicity, height, and weight.

### 12.4 STATISTICAL ANALYSIS PLAN (SAP)

The majority of 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 following operatory procedures. The SAP however, can include

investigation into individual vital sign parameters that the CM-1500 device (or another source) produces during a subject's recovery.

Analysis of data sets collected from all subjects aim to satisfy the following purposes, included but not limited to:

- [redacted]Examine, on a case by case review basis, the results produced by the CM-1500 device for relevant subject case results. [redacted]
- Classify aggregate results by subject outcomes, particularly nominal and hemhoragic shock/complications, and evaluate the performance of the CM-1500 to indicate either the presence of the presenting complication, or specify the absence of presenting complications.

[redacted]

# 13 DATA COLLECTION, RETENTION, AND MONITORING

## 13.1 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. Study personnel will enter data from source documents to protocol-specific electronic Case Report Forms (eCRF) or paper CRF. In some instances, CRF's will serve as source documentation. 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.

All Investigators are 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.

### 13.1.1 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 number, subject sex, subject age or year of birth will identify study subjects on CRFs and other documentation submitted to the Sponsor. A limited number of Sponsor representatives may have access to limited identifiable information and will take reasonable precautions to maintain the confidentiality of the subject's identity.

## 13.2 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.

## 13.3 MONITORING

### 13.3.1 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.

# 14 STUDY ADMINISTRATION

## 14.1 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.

## 14.2 PROTOCOL

### 14.2.1 STRUCTURE

The header of IRB approved documents will contain IRB Approval dates and amendment information. The footer, specifically, “Form” and “REV” are associated with template information, not IRB amendments.

### 14.2.2 PROTOCOL AMENDMENTS

Sponsor approval is required for any protocol amendment. Protocol amendments will not be implemented without prior written IRB approval except 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 at the time of the protocol amendment.

### 14.2.3 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).

## 14.3 INFORMED CONSENT FORM (ICF) AMENDMENTS

Sponsor approval is required for any ICF Amendment. ICF Amendments will not be implemented without prior written IRB approval.

# 15 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)).

15.1 INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC) REVIEW

The Protocol, ICF, and any subject facing material will be reviewed and approved by the IRB/EC prior to study initiation. 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. AE's and Protocol Deviations will be reported as applicable to the IRB and Sponsor. All IRB approvals will be kept in the Trial Master File, Investigator Site File, and copies will be sent to the Sponsor.

| | |
|---|---|
| IRB Name: | Wake Forest University Health Sciences<br>Office of Research Institutional Review Board |
| IRB Address: | Wake Forest University Health Sciences<br>Office of Research Institutional Review Board<br>Medical Center Boulevard<br>Winston-Salem, NC 27157-1023 |
| IRB Phone: | (336)716-4542 |
| IRB Email: | Not Applicable |
| IRB Registration #: | IORG0000129 |
| Federalwide Assurance #: | FWA0000143 |

15.2 INFORMED CONSENT WITH WAIVER OF DOCUMENTATION

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

A waiver of documentation is requested as the protocol meets 45 CFR 46.117(c)(1)(ii). The research is minimal risk, and a very limited protected health information ("PHI") will be collected as part of this study. De-identified verbal consent will be documented by the Investigator or qualified designated study personnel.

Assent 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 verbal consent to meet the Inclusion/exclusion criteria.

[redacted]

1. Mañas-Gómez MJ, Rodríguez-Revuelto R, Balsells-Valls J, et al. Post-pancreaticoduodenectomy hemorrhage. Incidence, diagnosis, and

treatment. *World J Surg*. 2011;35(11):2543-2548. doi:10.1007/s00268-011-1222-4

2. Ansari D, Tingstedt B, Lindell G, Keussen I, Ansari D, Andersson R. Hemorrhage after Major Pancreatic Resection: Incidence, Risk Factors, Management, and Outcome. *Scand J Surg*. 2017;106(1):47-53. doi:10.1177/1457496916631854

[redacted]

[redacted]