Intraoperative Warming During Major Surgical Procedures Using the Esophageal Temperature Management System (EnsoETM)

Protocol Number: 1.0

Principal Investigator: Coleen Vernick, DO

Co-Investigators:

Eric Schwenk, MD,

Michael Mahla, MD,

Mark Berguson, MD,

Marc C Torjman, PhD

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Signature Page

The signatures below constitute the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

STATEMENT OF COMPLIANCE

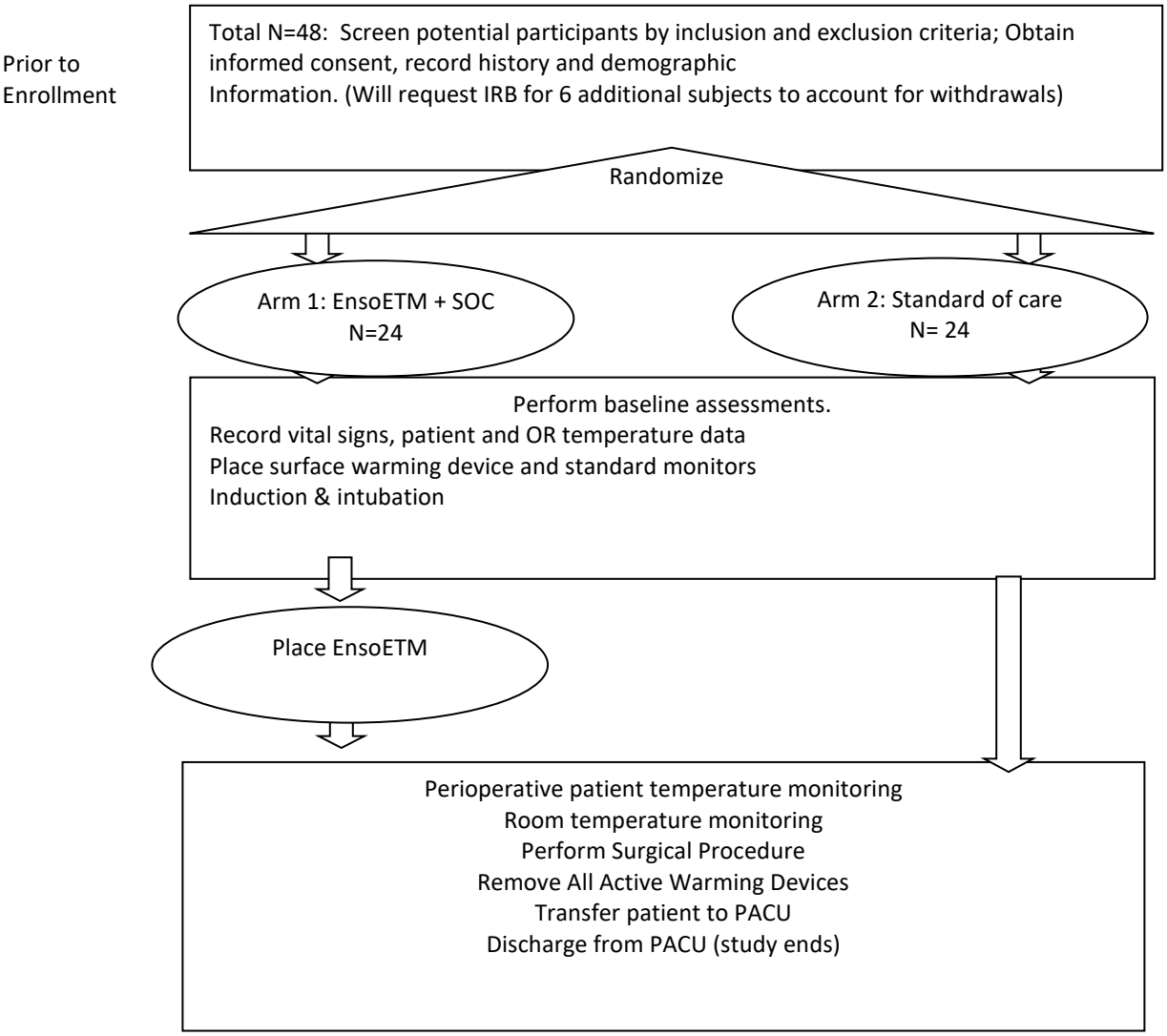
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Intraoperative Warming During Long Major Surgical Procedures **Using an Esophageal Temperature Management** System (EnsoETM)
Objectives:	Primary Objective: **The aim of this study is to assess the effectiveness of EnsoETM as a supplemental warming device compared to the standard of care warming practice in patients having major surgery.** Secondary Objectives: Compare clinical outcome variables between the two warming techniques
Endpoints:	Primary Endpoint: **The primary outcome is the number of degree-hours spent below 37 °C intraoperatively until recovery in the PACU and return to 37°C body temperature.** Secondary Endpoints: **A comparison will be made between the 2 groups** in blood loss, time to extubation, PACU temperature, and routine pain scores post-surgery.
Study Population:	Patient population will consist of adult male and female patients undergoing a surgical procedure expected to last ≥ 3 hours
Description of Sites/Facilities Enrolling Participants:	This study will take place at Thomas Jefferson University Hospital located at 111 South 11th Street, Philadelphia PA 19107
Description of Study Intervention:	Patients having major surgery will have the EnsoETM device placed after induction of general anesthesia, in addition to standard of care warming practices.
Study Duration:	Up to 24h, from patient entry into the OR until discharge from the PACU
Participant Duration:	The study subject will be in the study from time of the pre-op consult until discharge from the PACU.

1.2 SCHEMA


Prior to Enrollment
Total N=48: Screen potential participants by inclusion and exclusion criteria; Obtain informed consent, record history and demographic Information. (Will request IRB for 6 additional subjects to account for withdrawals)
Randomize
Arm 1: EnsoETM + SOC N=24
Arm 2: Standard of care N= 24
Perform baseline assessments.
Record vital signs, patient and OR temperature data
Place surface warming device and standard monitors
Induction & intubation
Place EnsoETM
Perioperative patient temperature monitoring
Room temperature monitoring
Perform Surgical Procedure
Remove All Active Warming Devices
Transfer patient to PACU
Discharge from PACU (study ends)

1.3 SCHEDULE OF ACTIVITIES

Procedures	Day -14 to -1	Day 0, Surgical Procedure	Day 0, PACU
Pre-Screening	X		
Informed consent		X	
Demographics	X		
Medical history	X	X	
Randomization		X	
Active Warming		X	
Vital signs		X	X
Height		X	
Weight	X	X	
Pregnancy test		X	
Adverse event review and evaluation		X	X
Temperature assessments		X	X
Complete Case Report Forms (CRFs)		X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Maintaining patient's body temperature is of major importance in patients undergoing surgical procedures and existing methods to warm patients to maintain perioperative normothermia have limitations. This results in as many as half of patients undergoing surgery developing inadvertent hypothermia during and/or after their procedure. Because surface covers, such as forced-air warming mattresses, cannot be used to cover a patient requiring exposure for surgery, and because under-body warming is unable to transfer significant heat to the patient without also heating operating staff surrounding the patient, a gap exists in the clinical need to warm complex surgical patients. The EnsoETM is an Esophageal Temperature Management (ETM) device consisting of a multi-chambered silicone tube connected to a heat exchanger and placed in the esophagus, providing highly efficient heat transfer to a patient. The EnsoETM potentially improves the ability to control patient temperature by eliminating the disadvantages of existing methods while maintaining the functionality of the orogastric tube that it replaces.

2.2 BACKGROUND

The ability to control a patient's body temperature under a wide variety of conditions is extremely important, and is of particular importance for the maintenance of normothermia during surgery. Unplanned decreases in body temperature of 1°C or more during surgery (referred to as inadvertent perioperative hypothermia) lead to multiple adverse outcomes. These adverse outcomes include a three-fold increase in surgical wound infections,[1,2] a three-fold increase in morbid myocardial complications,[3,4] increased blood loss and transfusion requirements,[5-12] increased mortality,[13-15] prolonged recovery and hospitalization,[1,16] and the development of shivering and thermal discomfort.[17] Despite efforts to date, the incidence of inadvertent perioperative hypothermia remains high, occurring in 30% to 70% of all surgical procedures lasting longer than 1 hour.[11,12,18-23]

To date, however, available modalities for maintaining normothermia have a number of technical and logistical barriers. Surface devices, which include various configurations of blankets, covers, or pads, are of limited efficacy in complex and lengthy surgical procedures due to the difficulties inherent in transferring heat across the available skin surface (which itself is limited by the need to expose the patient in order to allow the surgeon to operate).[24-30] Intravascular devices are able to provide a greater quantity of heat to the patient's core, but are invasive, expensive, and need to be sterile, with placement requiring access to a major blood vessel by a specially trained physician, and risks that include bloodstream infections and blood clots.[31-35] The EnsoETM is a simple disposable device that improves the effectiveness of temperature maintenance while minimizing the risks of other existing or invasive methods.[36] The EnsoETM (shown in Figure 1 and Figure 2) is a multichambered silicone tube connected to a heat exchanger (there are EnsoETM models currently cleared for use with the Stryker Altrix, Stryker/Gaymar Meditherm III, Cincinnati Sub-Zero Blanketrol II and III, and Cincinnati Sub-Zero Normotemp) that is placed in the esophagus to provide highly efficient heat transfer to a patient while simultaneously maintaining access to the stomach to allow gastric suctioning, decompression, and drainage, as usually performed in such patients undergoing surgical procedures in the operating room.

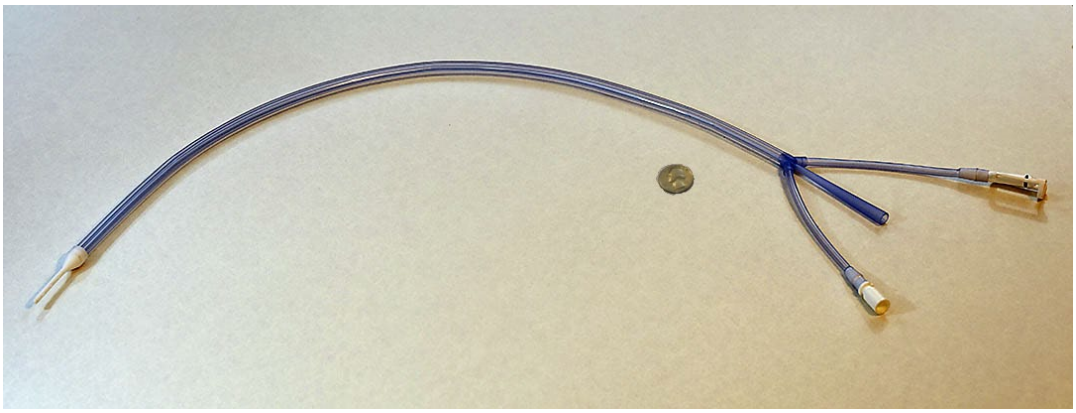


Figure 1. Photograph of the EnsoETM.

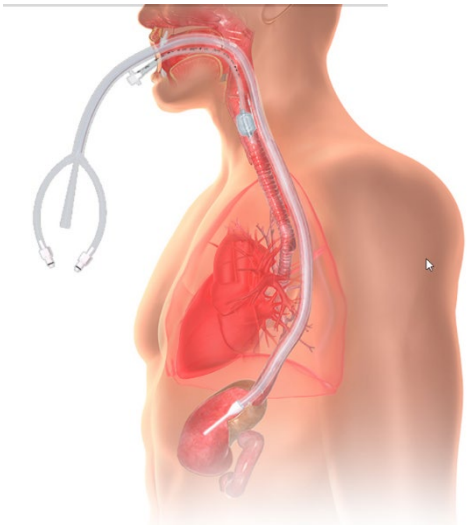


Figure 2. The EnsoETM shown in place in the esophagus (replacing the routine gastric tube placed in the target population as a standard of care), and located behind the trachea (containing the endotracheal tube which is placed in the trachea routinely to provide ventilation in the target patient population).

The esophagus is in close proximity to blood flow from the heart and great vessels, and the EnsoETM is designed to take advantage of this heat exchange environment. The EnsoETM's ability to decompress the stomach and avoid distention of the esophagus away from the device ensures good contact with the esophageal mucosa, and thus maximizes heat transfer between the device and the patient. The EnsoETM replaces the standard gastric tube which is placed in the target patient population as a routine standard of care, is made of standard medical-grade silicone, and is generally similar in shape to gastric tubes currently used, and similar in size to other devices routinely placed in the esophagus (esophagogastroduodenoscopy scopes, transesophageal echocardiography scopes, Ewald tubes). The EnsoETM is approximately 1/3rd the size of a Sengstaken–Blakemore tube used for the management of esophageal varices. A growing number of clinical studies have shown strong support for the efficacy and safety of the EnsoETM.[37-48]

The proposed study will be the first randomized control trial measuring patient warming during a long surgical procedure. Previous studies evaluated device performance when cooling for therapeutic hypothermia and refractive pyrexia reversal in critical care settings.[38,39,49-54] One small case series documented warming in 3 severe burn patients[55] and a small feasibility trial aimed to quantify heating and cooling capacity in the general surgical population.[56]

3 OBJECTIVES AND ENDPOINTS

The primary objective of this study is to measure the number of degree-hours spent below 37°C intraoperatively and until transfer to the PACU. This measure will be compared between patients having standard management of body temperature to patients having the EnsoETM placed as an additional warming device.

4 STUDY DESIGN

This is a single site prospective, randomized interventional study evaluating the ability of the EnsoETM to reduce the amount of time a patient spends below 37°C when added to usual care. Control patients will have standard temperature management, while the experimental arm will have standard temperature management with the addition of the EnsoETM. Patients eligible will be those patients having major surgical procedures of long duration.

We hypothesize that:

1. Patients warmed with the addition of the EnsoETM will demonstrate at least a 20% relative decrease in the amount of time spent below 37°C, as measured in degree-hours, when compared to controls.
2. Patients warmed with the EnsoETM will demonstrate equivalence with standard of care warming procedures across clinical outcomes, including: transfusion volume, time to extubation, temperature maintenance after surgery, and routine pain scores.

5 METHODS

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Male or female, ages 18 years and older
3. Scheduled for major surgical procedures requiring general anesthesia and with no known contraindication to having an orogastric tube placed for the duration of the surgery
4. Expected OR time greater than or equal to 180 minutes

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5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Esophageal strictures
2. Patients with known esophageal deformity or evidence of esophageal trauma (for example history of esophagectomy, previous swallowing disorders, achalasia, etc.)
3. Known ingestion of acidic or caustic poisons within the prior 24 hours.
4. Patients with <40 kg of body mass
5. Known coagulopathy
6. Severe facial trauma
7. Expected OR time less than 180 minutes

5.3 STUDY PROCEDURES

Subjects will be pre-screened by the study coordinator based on the surgical schedule (typically within 14 days of the scheduled surgery date). The patient record will then be reviewed by an investigator to confirm eligibility. If eligible, the study coordinator will contact the potential subject by phone to invite participation, explain the study, answer any preliminary questions, and offer to provide the ICF for review. If patients indicate they do not wish to participate in this study, they will not be approached again. On the morning of the surgery, the investigator will review the study and ICF a second time, answer any questions about the study, and obtain a signature on the ICF. Upon obtaining consent for participation in research (independent from patient consent for the surgical procedure), the patient will be randomized.

Patients will be randomized according to a randomization table (developed by using a random number generator) and constructed prior to first patient enrollment. After the participant consents and is assigned an ID, the clinical coordinator will inform the investigator of the experimental condition indicated. If patients are withdrawn from the study before the surgical procedure is completed, additional patients will be randomized at the end of the study until both groups are complete.

As per standard procedure, preoperative vital signs and temperature will be obtained in the patient holding area. The study subject will be brought to the operating room and standard monitors will be applied. Initial temperatures will be measured via the usual institutional temperature measurement preference and recorded. Upon entering the OR, patients in both groups will be warmed using the standard warming device used at Thomas Jefferson University Hospital (Bair Hugger^{TM}) according to standard practice, throughout the surgical procedure.

All patients will also receive warmed fluids during the OR procedure; fluid warmer settings and volumes will be noted in the patient chart and CRF.

Patients assigned to the intervention group will have an EnsoETM placed into the esophagus following induction of general anesthesia and intubation of the trachea and the heat exchange unit will be set to warming mode (42°C). The EnsoETM will remain in place with water circulation set to 42°C during patient positioning, while all monitors are placed, and the patient is prepared for the surgery. The Bair Hugger and EnsoETM temperatures will be adjusted as necessary to maintain the patient's body temperature at 37°C. All adjustments will be noted in the CRF.

Continuous temperature measurements specifically during surgery will be measured by one of the following: bladder temperature sensors, forehead sensors (3M SpotOn), reliable tympanic membrane sensor, or rectal temperature sensors. Nasopharyngeal or esophageal temperature measurement is not recommended due to interference by the EnsoETM. Time of anesthesia induction, time of EnsoETM placement, and room ambient temperature will be recorded.

The target temperature for both groups will be 37°C. The temperature data will be recorded continuously and times for each external temperature adjustment to the Blanketrol or Bair Hugger will be recorded manually.

The patient's anesthetic management in both arms will follow standard of care and consist of general endotracheal anesthesia. Rocuronium or succinylcholine will be used for providing muscle relaxation as indicated. Ketamine may be administered in chronic opioid users. Hemodynamic management and fluid maintenance and replacement will be based on clinical indication at the discretion of the attending anesthesiologist.

5.4 RISK/BENEFIT ASSESSMENT

5.4.1 Known Potential Risks

Placing the EnsoETM is a minimal risk procedure with no contraindications. The construction of the device and insertion technique are very similar to that of a standard orogastic tube. The EnsoETM device has been placed in approximately 5000 critical care patients globally, without any documented serious injury. However, the potential risks of insertion of a standard orogastric tube (which are placed millions of times per year) include:

- May cause laryngeal injury during insertion
- The gastric tube may be misplaced into the trachea
- Insertion of the tube could cause esophageal perforation (there have been no reports of accidental intubation with use of this device)

Any device placed into the esophagus can, in rare cases, cause perforation or laryngeal injury, including standard OG tubes, NG tubes, and bougies. This study minimizes this risk by excluding patients with known esophageal deformity or injury.

Since the device Instructions for Use (IFU) do not indicate that the patient must be intubated when the ETM is placed, there are circumstances where the ETM could be misplaced in the trachea. This is true for other routine-use devices intended for esophageal placement when the airway may not be secure, such as OG and NG tubes. In this study, the patients will be intubated prior to insertion, so that risk is fully mitigated. There are currently no documented cases of the ETM being misplaced in the trachea.

5.4.2 Known Potential Benefits

Prospective, randomized trials have shown that even mild hypothermia causes numerous adverse outcomes in a variety of patient populations. Hypothermia-induced complications include morbid myocardial outcomes[22] secondary to sympathetic nervous system activation, [23] surgical wound infection,[24,25] coagulopathy[6,26-33] increased allogeneic transfusions,[6, 24,26,27,31,33-37] negative nitrogen

balance,[38] delayed wound healing,[24] delayed postanesthetic recovery,[39] prolonged hospitalization,[24] shivering,[40] and patient discomfort.[41] The potential for improved temperature management during surgery with the addition of the EnsoETM device could benefit the subject. However, subjects may not receive a direct benefit from being in this research study. Society in general may benefit (in the future) if this research leads to improved temperature management during surgery with the addition of the EnsoETM device.

5.5 END OF STUDY DEFINITION

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- The study subject will be considered completed once the patient is discharge from the PACU.

5.6 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

5.7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events are categorized as defined in ISO 14155:
Adverse event (AE): Any untoward medical occurrence in a subject
Note: this definition does not imply that there is a relationship between the AE and the device under investigation
Adverse device event (ADE): Any untoward and unintended response to a medical device.
Note 1: this definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.
Note 2: this definition includes any event that is a result of a user error
Serious adverse event (SAE): Adverse event that:

1. Lead to a death
2. Lead to a serious deterioration in the health of the subject:
   - resulted in a life-threatening illness or injury
   - resulted in a permanent impairment of a body structure or a body function
   - required in-patient hospitalization or prolongation of existing hospitalization
   - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
3. Lead to fetal distress, fetal death or a congenital abnormality or birth defect

Serious adverse device event (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.
Note: The Investigator is responsible for any reporting requirements to the local government or Ethics Committee.
Unanticipated serious adverse device event (USADE): is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report
Note: Anticipated serious device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

5.8 ANTICIPATED ADVERSE EVENTS AND DEVICE EFFECTS

The safety of the EnsoETM has been established through post-market surveillance. However, during the study, the following potential adverse events may occur.

1) Failure to insert the study device. Though patients are screened for known esophageal deformities or injury, asymptomatic anatomical variations do occur that make esophageal insertion (of any device) challenging. If on visualizing the oropharynx the investigator observes an anatomical variation that might hinder study device insertion or experiences unusual resistance (as compared to routine OG tube placement) to advancing the study device into the stomach, the study device should not be inserted and the patient should be withdrawn from the study.

2) External equipment failure. Though new external heat exchange units will be dedicated to this study, mechanical failure is still possible. The heat exchange unit has several audible and visual alerts that each investigator and study coordinator will be trained to respond to. If the issue cannot be quickly addressed, the study device should be removed and the patient should be withdrawn from the study.

3) Device leak during a procedure. If a study device is punctured during the procedure causing a distilled water leak, the investigator, at his or her discretion, may elect to replace the device during the procedure or withdraw a patient if a new study device is not readily available.

4) If the surgical procedure is suspended prematurely for any reason, whether or not the cause is device-related (for example, the patient responds poorly to anesthesia), the patient should be withdrawn from the study.

In the event of an adverse event related to device performance, the study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible no later than 5 business days in accordance with the Thomas Jefferson University IRB.

For this study, the period during which adverse events must be reported is defined as the period from the initiation of any study procedures (consent) to the end of the study follow-up (PACU discharge). Adverse events that do not require expedited reporting will be reported in summary to the IRB at continuing review.

6 STATISTICAL CONSIDERATIONS

After discussion with several anesthesiologists the general opinion was that achieving 37°C for long major surgical procedures is often not possible with the current warming devices. A technology that could allow maintenance of normothermia for most of the case would be acceptable considering that temperatures will sometimes drop 2 to 3 °C below 37 °C. We therefore based the power analysis using assumptions derived from those discussions which we believe most anesthesiologists would support.

6.1 SAMPLE SIZE DETERMINATION

The assumption for determination of sample size was based on a majority of patients (≥70%) in the EnsoETM arm demonstrating at least a 20% relative decrease in the amount of time spent below 37 C, as measured in degree-hours, when compared to controls. The power analysis used a test of equality of proportions assuming that a minimum of 40% more patients in the EnsoETM group would achieve a 20% relative decrease in the amount of time spent below 37 C, as measured in degree-hours. With the criterion for significance (alpha) set at 0.05 and a power of 80% the study will require 24 patients in each group (N=48). For this study we will request the IRB for 6 additional patients to account for withdrawals due to technical problems or clinical necessity.

6.2 STATISTICAL ANALYSES

Descriptive statistics will be performed to examine patient demographic data. Summary tables with appropriate measures; means, SD, medians, IQR, and 95% confidence intervals will be generated for patient characteristic and clinical variables for each group. Statistical tests will be performed to determine significance between the groups. Demographic

data and primary and secondary objective variables will be analyzed using ANOVA, Logistic Regression Analysis, Chi-Square, Kruskal Wallis, and Student t tests as indicated.

7 STUDY ADMINISTRATION, DATA HANDLING AND RECORD KEEPING

7.1 CONFIDENTIALITY

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

7.2 DATA COLLECTION AND MANAGEMENT

Data will be collected by trained research staff using paper-based screening tools and electronic source documents. Source documents will be recorded on a Sponsor-provided laptop. Participants will be assigned a Participant ID "PID" for use on data collection in for entry into the DMS to protect and ensure confidentiality.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study data will be stored indefinitely. A de-identified data set may be shared with the funding sponsor.

7.3 RECORDS RETENTION

Study records, including administrative and participant related source and CRFs, will be retained for 2 years after the completion of the research (often marked by a final progress report).

8 STUDY MONITORING, AUDITING, AND INSPECTING

8.1 STUDY MONITORING PLAN

The investigator and research team will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. clinical ORs), and has adequate space to conduct the monitoring visit.

8.2 AUDITING AND INSPECTING

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

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