Core Warming of COVID-19 Patients Undergoing Mechanical Ventilation: *A Randomized, Single Center Pilot Study*

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Study Device:	Attune Medical esophageal heat transfer device - ensoETM
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List of Abbreviations

AE: Adverse event

ARDS: Acute Respiratory Distress Syndrome

COVID-19: Coronavirus disease 2019

EMR: Electronic Medical Record

ICU: Intensive Care Unit

SAE: Serious adverse event

SARS-CoV-2: Etiology of coronavirus disease 2019

SOC: Standard of care

SOFA Score: Sequential Organ Failure Assessment Score

Study Summary

Title	Core Warming of COVID-19 Patients Undergoing Mechanical Ventilation: a randomized, single center pilot study
Short Title	COVID Core Warming
IRB Number	*Pending*
Phase	Pilot Study
Methodology	Randomized, single center pilot study
Study Duration	Approximately 3-5 months
Study Center	Sharp Memorial Hospital
Objectives	Primary: • Determine the change in PaO2/FiO2 ratio at 0, 24, 48, and 72 hours after implementation of core warming of ventilated patients, and compare this change to patients undergoing standard care. Secondary: • Determine the change in viral load measured in nasopharyngeal swab by Cycle Threshold at 0, 24, 48, and 72 hours after implementation of core warming of ventilated patients, and compare this change to patients undergoing standard care. • Measure the impact of core warming on duration of mechanical ventilation. • Determine impact of core warming on patient mortality.
Number of Participants	22
Length of Participation	72 hour intervention phase; 30 day follow up

Inclusion Criteria	1. Patients above the age of 18 years old. 2. Patients with the diagnosis of COVID-19 requiring mechanical ventilation. 3. Patient maximum baseline temperature (within previous 12 hours) < 38.3°C. 4. Patients must have surrogate or legally authorized representative able to understand and critically review the informed consent form.
Exclusion Criteria	1. Patients without surrogate or legally authorized representative able to provide informed consent. 2. Patients with contraindication to core warming using an esophageal core warming device. 3. Patients known to be pregnant. 4. Patients with <40 kg of body mass. 5. Patients with DNR status. 6. Patients with acute stroke, post-cardiac arrest, or multiple sclerosis.
Investigational Device	Attune Medical esophageal heat transfer device – ensoETM. Used as indicated for patient temperature management.
Duration of administration	72 hours
Reference therapy	Standard temperature management as routine at study site
Statistical Methodology	A total of 11 patients for each group will be required to yield the necessary pilot data regarding the feasibility and effect of core warming on viral load and ventilation requirements.
Safety Evaluations	Standard adverse event monitoring (device is in widespread use for patient warming and cooling).
Data and Safety Monitoring Plan	The PI and research team will be responsible for data and safety monitoring.

This study will be conducted in full accordance with all applicable study site research policies and procedures and all applicable federal and state laws and regulations.

1.0 Background and Study Rationale

1.1 Introduction

Traditionally, fever has been treated because its metabolic costs were felt to outweigh its potential physiologic benefit in an already stressed host.[1] However, increasing data suggest that fever may be a protective adaptive response that should be allowed to run its course under most circumstances.[2, 3] Although one randomized controlled trial using physical cooling of mechanically ventilated patients with septic shock found a reduction in vasopressor dose and reduced early mortality when treating fever,[4] a growing number of studies have found either no clinically important benefit, or harms, in treating fever of infectious origin.

1.2 Background and Relevant Literature

Studies have found that higher early fever is associated with a lower risk of death among patients with an ICU admission diagnosis of infection [5, 6] and that fever may enhance immune-cell function,[7, 8] inhibit pathogen growth,[9-11] and increase the activity of antimicrobial drugs.[12] Fever potentially benefits infected patients via multiple mechanisms; in vitro and animal studies have shown that elevated temperatures augment immune function, increase production of protective heat shock proteins, directly inhibit microorganism growth, reduce viral replication, and enhance antibiotic effectiveness.[3, 13] More rapid recoveries are observed from chickenpox,[14] malaria,[15] and rhinovirus [16] infections with avoidance of antipyretic medication, and many innate and adaptive immunological processes are accelerated by fever.[17-19] The UK National Institute for Health and Care Excellence (NICE) recommend not using antipyretic agents “with the sole aim of reducing body temperature in children with fever.”[17, 20] As recently as the 1910’s, the “malaria fever cure” (inducing fever to treat a range of conditions, an approach known as “pyrotherapy”) was widespread, with the originator of the idea receiving the Nobel Prize in Medicine or Physiology in 1927.[21, 22]

A randomized control trial published in 2005 evaluating the impact of antipyretic therapy on outcomes in critically ill patients had to be terminated at the interim analysis as there were seven deaths in the aggressive group and only one death in the permissive group.[23] Another randomized controlled trial in critically ill patients (without neurotrauma or severe hypoxia) failed to support the treatment of fever; no significant differences in ICU and hospital length of stay, or mortality between those receiving external cooling for temperature ≥38.5 ℃ vs. no antipyretic treatment was found.[24] A prospective controlled trial randomized 700 patients with fever of known or suspected infectious etiology to receive either 1 g of intravenous acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death.[25] The primary outcome, ICU-free days until day 28, was not decreased in the treatment arm, and secondary outcomes (28 and 90-day mortality, ICU and hospital length of stay) were also not significantly different between groups.[25]

A systematic review and trial sequential analysis of randomized controlled trials found a total of 6 randomized controlled trials including 819 patients.[26] Overall, there was no beneficial effect of antipyretic therapy on mortality risk in patients with established sepsis (OR: 1.02, 95% CI:

0.50–2.05), and the review failed to identify any beneficial effect of antipyretic therapy on ICU patients with established diagnosis of sepsis.[26] Another systematic review and meta-analysis of randomised controlled trials investigating treatments administered to febrile patients found fifteen studies reporting results from 13 trials, and found that active temperature management neither increased nor decreased mortality risk, ICU, or hospital length of stay in critically ill adults.[27] A meta-analysis examining the impact of antipyretic therapy on mortality in critically ill septic adults found 8 randomized studies (1,507 patients) and 8 observational studies (17,432 patients).[28] Antipyretic therapy did not reduce 28-day/hospital mortality in the randomized studies (relative risk, 0.93; 95% CI, 0.77–1.13; I2 = 0.0%) or observational studies (odds ratio, 0.90; 95% CI, 0.54–1.51; I2 = 76.1%), and the authors concluded that antipyretic treatment does not significantly improve 28-day/hospital mortality in adult patients with sepsis.[28]

A retrospective cohort study evaluated 1,264 patients requiring mechanical ventilation initiated in the ED with subsequent admission to an intensive care unit.[29] The authors found that high fever (≥39.5°C) was associated with increased risk for mortality in mechanically ventilated patients; however, in patients with sepsis, moderate fever (38.3°C-39.4°C) was protective, and antipyretic medication was not associated with changes in outcome.[29] An open, parallel-group pilot randomized clinical trial (the FEVER pilot trial) enrolled 87 pediatric intensive care unit patients who were randomly assigned to permissive (antipyretic interventions only at ≥ 39.5 °C) or restrictive groups (antipyretic interventions at ≥ 37.5 °C) whilst on respiratory support.[17] Length of stay, duration of organ support and mortality were similar between groups, and no pre-specified serious adverse events occurred.[17] Finally, a pilot study of external warming of septic patients (ClinicalTrials.gov Identifier: NCT02706275) has recently been completed, with initial analysis of results appearing promising (manuscript in preparation).

Temperature has been suggested to influence the virulence of an earlier discovered coronavirus, SARS CoV, [30] and most isolates of human rhinovirus, the common cold virus, replicate more robustly at the cool temperatures found in the nasal cavity (33–35 °C) than at core body (lung) temperature (37 °C).[31] Rhinovirus replicates preferentially at cooler nasal cavity temperature due, in part, to a less efficient antiviral defense response of infected cells at cool temperature, raising the possibility that inhaling cool air might diminish resistance to respiratory virus infections by lowering the temperature of potential host cells lining the nasal cavity.[31] Influenza

B virus viral hemagglutinin exhibits higher expression at 33°C (a temperature required for membrane fusion), indicating pronounced adaptation to the mildly acidic pH and cooler temperature of human upper airways.[32] Specifically, protein expression of influenza B virus viral hemagglutinin proved to be temperature dependent, with expression highest at 33°C and gradually decreasing at higher temperatures.[32] On the other hand, avian influenza A viruses, adapted to the temperature of the avian enteric tract (40°C), show restricted growth at cooler temperatures (~32°C).[32]
More recently, simulations of the receptor binding domain (RBD) of SARS-CoV-2 found that it is more flexible than SARS CoV, especially near the binding site, suggesting that the RBD will have a higher entropy penalty upon binding angiotensin-converting enzyme II (ACE2) compared to the RBD of SARS-CoV.[33] Consequently, SARS-CoV-2 may be more temperature-sensitive in terms of human infection than SARS-CoV.[33]

Hyperthermia induced by directly heating the body (as opposed to fever induced by introducing bacterial extracts or other foreign substances) is normally limited to 41.8 to 42°C when used to kill tumor cells in cancer treatment, with minimal adverse effects.[34-37] Furthermore, hyperthermia and elevated temperature have been found to have positive impacts on the immune system. Cells have been found to exhibit increased levels of heat-shock proteins, specifically HSP70 [38] and HSP90, [39] which are directly related to and/or cause antigen presentation and cross-presentation, activation of macrophages and lymphocytes, and activation and maturation of dendritic cells,[40] all of which are essential antiviral immune responses. Notably, fever has often abated by the time a COVID-19 patient requires mechanical ventilation.[41]

The aim of this study is to determine the effect of active core warming patients diagnosed with COVID-19 and undergoing mechanical ventilation. We hypothesize that active core warming will reduce the severity of acute respiratory distress syndrome, reduce the duration of mechanical ventilation, and improve survival compared to standard of care.

1.3 Name and Description of the Core Warming Device

Core warming will be performed using an esophageal heat transfer device (ensoETM, Attune Medical, Chicago, IL) This device is an FDA cleared device, and is a multi-lumen silicone tube placed in the esophagus for the purpose of cooling or warming a patient while simultaneously allowing gastric decompression and drainage. Modulation and control of the patient's temperature is achieved by connecting the device to an external heat exchanger. Two lumens connect to the external heat exchanger, while a third central lumen provides stomach access for connection to a fluid collection device with low intermittent suction for gastric decompression. Distilled water circulates within the device just like a water blanket. The device can be placed by most providers in the operating room, emergency room, or intensive care unit. It is a single-use, disposable, non-implantable device with an intended duration of use of 72 hours or less. For this study, the device will be used during mechanical ventilation of patients with diagnosed COVID-19, under the intended indication of patient temperature management as detailed in the product instructions for use.

1.3.1 Clinical Data to Date

Core warming and cooling has been used safely in thousands of patients for temperature control, making it the ideal approach to use for this study. Core cooling or warming using an esophageal heat transfer device is used for a range of temperature management purposes, including post-cardiac arrest therapeutic hypothermia [42-45], warming of burn patients [46], warming general surgical patients,[47] cooling traumatic brain injury,[48] cooling heat stroke,[49] and the treatment of central fever.[50, 51]

2 Study Objectives

The purpose of the proposed pilot study is to determine if core warming improves respiratory physiology of mechanically ventilated patients with COVID-19, allowing earlier weaning from ventilation, and greater overall survival.

2.1 Primary Objectives

1. Determine the change in PaO2/FiO2 ratio at 0, 24, 48, and 72 hours after implementation of core warming of ventilated patients, and compare this change to patients undergoing standard care.

2.2 Secondary Objectives

1. Determine the change in viral load measured in nasopharyngeal swab by Cycle Threshold at 0, 24, 48, and 72 hours after implementation of core warming of ventilated patients, and compare this change to patients undergoing standard care.
2. Measure the impact of core warming on duration of mechanical ventilation.
3. Determine impact of core warming on patient mortality.

3 Investigational Plan

3.1 General Design

This is a small scale pilot study to evaluate if core warming improves respiratory physiology of mechanically ventilated patients with COVID-19, allowing earlier weaning from ventilation, and greater overall survival. This prospective, randomized study will include 22 patients diagnosed with COVID-19, and undergoing mechanical ventilation for the treatment of respiratory failure. Patients will be randomized in a 1:1 fashion with 11 patients (Group A) randomized to undergo core warming, and the other 11 patients (Group B) serving as the control group who will not have the ensoETM device used. Patients randomized to Group A will have core warming initiated in the ICU or other clinical environment in which they are being treated after enrollment and provision of informed consent from appropriate surrogate or legally authorized representative.

3.1.1 Screening Phase

Subjects will be recruited from the ICU or other clinical environment in which they are being treated (Emergency Department, step-down unit, etc.). Patients will be identified by the PI or other study investigators/coordinators as available. All patients without a DNR order with a diagnosis of COVID-19 and meeting inclusion criteria will be eligible for screening for any exclusion criteria. Written informed consent for the research study will be obtained from patient's surrogate or legally authorized representative prior to enrollment.

3.1.2 Study Intervention Phase

Participants who have a signed research study consent form (via surrogate or legally authorized representative) will be randomized in a 1:1 fashion to core warming with the study device (ensoETM) or to standard of care (standard temperature management and treatment). The device will be used as indicated (for warming). Patient temperature measurement will be collected for both the core warming and standard of care arms during the study period (72 hours).

Core warming will be performed using standard technique per instructions for use for the esophageal heat transfer device. The esophageal heat transfer device will be set to 42°C temperature after initial placement, and maintained at 42°C for the duration of treatment. It is expected that patient temperature will increase from baseline by 1°C to 2°C, but due to ongoing

heat loss from the patient, the expected maximum patient temperature is below 39°C. The time course of illness of COVID-19 is such that most patients no longer have fever by the time of mechanical ventilation.[41] If patient temperature increases above this range and reaches 39.8°C, the device will be set to an operating temperature of 40°C, thereby preventing any further increase in patient temperature (ambient heat loss precludes patient from reaching device operating temperature).

Monitoring and Evaluation

All patients will have usual standard of care labs, vital signs, and imaging for patients undergoing mechanical ventilation in the ICU. Specific parameters to be measured include PaO2 at regular intervals appropriate for patients undergoing mechanical ventilation, and FiO2 at the time of obtaining blood gases for PaO2 measurement, to allow calculation of P/F ratio.

3.1.3 *Follow Up (Day 30)*

Follow up data will be collected at 30 days following initiation of study treatment.

3.1.4 Allocation to Interventional Group

The randomization algorithm will be built into the electronic data capture system, Redcap, which will be used to collect data in the study. Once the randomization form is entered into the system and saved, the back end algorithm will run and a participant will be assigned an arm corresponding to either study device (Group A – Core warming) or standard of care (Group B – Control). Patients will undergo randomization after being enrolled into the study and prior to the placement of the core warming device. Randomization will be performed in a 1:1 fashion and maintained on the limited access, encrypted, Redcap database.

3.2 Study Endpoints

The purpose of the proposed pilot study is to determine if core warming reduces the severity of acute respiratory distress syndrome as measured by PaO2/FiO2 ratio 72 hours after initiation.

3.2.1 Primary Study Endpoints

The primary endpoint of this study will be:

1. PaO2/FiO2 ratio at 0, 24, 48, and 72 hours after initiation of core warming

3.2.2 Secondary Study Endpoints

1. Viral load measured in nasopharyngeal swab by Cycle Threshold at 0, 24, 48, and 72 hours after initiation of core warming
2. Duration of mechanical ventilation
3. Mortality

4 Study Population and Duration of Participation

All patients will have a diagnosis of COVID-19 requiring mechanical ventilation. Duration of intervention will be 72 hours. Follow-up will be to 30 days.

4.1 Inclusion Criteria

1. Patients above the age of 18 years old.
2. Patients with a diagnosis of COVID-19 on mechanical ventilation.
3. Patient maximum baseline temperature (within previous 12 hours) < 38.3°C.

4. Patients must have a surrogate or legally authorized representative able to understand and critically review the informed consent form.

4.2 Exclusion Criteria

1. Patients without surrogate or legally authorized representative able to provide informed consent.
2. Patients with contraindication to core warming using an esophageal core warming device.
3. Patients known to be pregnant.
4. Patients with <40 kg of body mass.
5. Patients with DNR status.
6. Patients with acute stroke, post-cardiac arrest, or multiple sclerosis.

4.3 Subject Recruitment

Subjects will be recruited from the ICU or other clinical environment in which they are being treated (Emergency Department, step-down unit, etc.). Patients will be identified by the PI or other study investigators/coordinators as available. All patients without a DNR order with a diagnosis of COVID-19 and meeting inclusion criteria will be eligible for screening for any exclusion criteria. The study team will pre-screen the potential subject's EMR, to assess all other inclusion/exclusion criteria, prior to approaching the patient and/or their surrogate / legally authorized representative about study participation. Written informed consent for the research study will be obtained from patient's surrogate or legally authorized representative prior to enrollment. If a patient enrolled in the study gains the capacity to consent for him/herself while the study is in progress, the patient will be approached by a study team member and the consent document will be presented directly to the patient. All questions the patient might have will be answered. The patient will be given the opportunity to either withdraw from the study or sign the consent form. The patient will be informed that his or her decision to withdraw from the study will not affect his or her medical care

4.4 Duration of Study Participation

Participants will be involved for approximately 30 days, including screening, treatment, and follow-up. After consent, patient participation in the intervention phase will last 72 hours for active treatment. The follow up for determination of outcome and duration of mechanical ventilation will occur at 1-month post-treatment. Additional data will be collected via chart review.

4.5 Total Number of Subjects and Sites

Recruitment will end when 22 participants are randomized.

5 Study Intervention

5.1 Intervention Regimen

Patients who are randomized to core warming will have the esophageal heat transfer device placed in the ICU or other treatment area where patient is undergoing mechanical ventilation. The device will remain in place until the study is completed (72 hours). The device will be set to 42°C for the duration of the study period, with the exception of any elevations in patient temperature as described in section 3 above.

5.2 Blinding

Due to the nature of this study, the physicians will not be blinded to the randomization assignment, however participants will be blinded. Once a subject is randomized, the research team will receive the randomization assignment (core warming or standard of care) and proceed with the procedures per the assignment.

5.3 Device Accountability

Core warming device accountability logs will be kept on file, will be completed on a regular basis, and will include product number, date of use, participant ID code, device damaged/destroyed and date of damage/destruction (including return date if applicable).

6 Schedule of Procedures and Data Extraction

Study Phase	**Screening**	**Randomization/ Intervention Phase**		**Follow up**
Study Days	**Day -1to 0**	**Day 0**	**Day 1-2**	**Day 30**
Informed Consent	X			
Review Inclusion/Exclusion Criteria	X			
Demographics	X			
Medical History/Interim History*	X			X
Physical Examination*	X		X	X
Vital Signs: Temperature, BP, HR, RR*	X	X	X	X
Height and Weight	X			
Pregnancy Test	X			
Clinical Labs	X	X	X	
Respiratory tract viral load		X	X	
Ventilator settings	X	X	X	
SOFA score	X	X	X	
Clinical Imaging (per routine)	X	X	X	
Prior/Concomitant Medications	X			X
Randomization		X		
Temperature monitoring		X	X	
PaO2, FiO2, parameter recording		X	X	
Adverse Event / Unanticipated Problems Assessment		X	X	X

* Interim medical history, physical exam, and vitals will be collected via chart review from routine clinical care.

6.1 Pre-Screening

Patients will be screened within 24 hours prior to the Baseline/Randomization timepoint to determine potential eligibility.

6.2 Study Visits & Data Collection

6.2.1 Screening, Enrollment, and Randomization

Study personnel will assess each subject against each inclusion and each exclusion criterion and the Investigator will determine the subject's eligibility for study participation. The principal

investigator or documented members of the research team will discuss the underlying rationale for the study, the procedures to be followed, the potential benefits and risks, and other issues mandated by the consent process with the surrogate or legally authorized representative. The participant's surrogate or legally authorized representative will be asked if they would like to participate, and if so, this will be documented using the study ICF. Determining the eligibility for each participant will require information generated during the course of routine clinical care as dictated by their attending physicians. Selected testing data will be collected in order to characterize the type, cause and severity of the patient's need for mechanical ventilation and the treatments received prior to enrollment. The data will include information from the evaluations listed below.

Once the Investigator has reviewed and signed the eligibility checklist, the research staff will enter the participant's information into the RedCap system to obtain the randomization assignment.

Data collection:

- Inclusion/Exclusion criteria review
- Study Informed Consent
- Collect Demographics (including sex/gender, race, ethnicity, and age via date of birth)
- Medical Record Review (including any history of disease, social history, physical exam findings and physicians notes)
- Review of Concurrent Medications
- Physical Exam
- Vital Signs: temperature, blood pressure, heart rate, respiration rate, height and weight
- Routine Clinical Labs/Phlebotomy such as a complete blood count (CBC) and chemistry profiles, along with most recent arterial blood gas for determination of PaO2, if collected as routine care.
- Specific labs recorded include: sodium, potassium, creatinine, hematocrit, white blood cell count, and CRP, if collected as routine care.
- Lower respiratory tract (tracheal aspirate, sputum) viral load (cycle threshold)
- SOFA score
- Ventilator settings
- Pregnancy test for women of childbearing potential
- Randomization
- Adverse Event/Unanticipated Problem assessment and recording

6.2.2 Post-placement

As part of routine monitoring, participants will have regularly obtained parameters (labs, vital signs, ventilator settings) recorded, as well as viral load at start and end of treatment.

- Interim medical history review
- Physical Exam
- Vital Signs: temperature, blood pressure, heart rate, respiration rate, height and weight

- Routine Clinical Labs/Phlebotomy such as a complete blood count (CBC) and chemistry profiles, along with most recent arterial blood gas for determination of PaO2, if collected as routine care.
- Specific labs recorded include: sodium, potassium, creatinine, hematocrit, white blood cell count, and CRP, if collected as routine care.
- Lower respiratory tract (tracheal aspirate, sputum) viral load (cycle threshold)
- Ventilator settings
- Adverse Event/Unanticipated Problem assessment and recording

6.2.3 Post treatment

Participant's clinical status and outcome will be reviewed 30 days after study completion.

The following procedures will be collected:

- Interim medical history review /concomitant medications
- Physical Exam & Vital Signs
- Adverse Event/Unanticipated Problem assessment and recording

6.3 Rescue Therapy

The core warming device will be removed and replaced if at any time there is evidence of a potential device malfunction. The device can be easily removed and replaced during treatment if needed. Should evidence of continued malfunction occur after replacement of the study device, the device will be removed, allowing the patient to undergo the standard of care with respect to temperature monitoring and control.

6.4 Unscheduled Visits

The research team will assess for the occurrence of any adverse event(s)/unanticipated problem(s) should a patient present for any unscheduled visit after discharge, up through 30 days following the study.

6.5 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study procedures or visit schedules, AEs, or should it become clinically necessary to deviate from the study protocol during the course of the study. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. We will attempt to have one final visit or contact to follow up regarding adverse events for participants who withdraw prior to the 30 day follow up visit.

6.5.1 Data Collection and Follow-up for Withdrawn Subjects

We will attempt to have one final visit or contact to follow up regarding adverse events for participants who withdraw prior to the 30 day follow up visit. During this contact they will be asked for permission to have the study team look into their survival status via their electronic medical records and publicly available means.

7 Statistical Plan

Primary Endpoint

The primary endpoint of this study will be the change in PaO2/FiO2 ratio at 0, 24, 48, and 72 hours after implementation of core warming of ventilated patients. This endpoint will be compared between patients receiving core warming and those randomized to undergo standard care (standard temperature management, with or without antipyretics as needed).

7.1 Secondary Endpoints

Secondary endpoints include:

1. Viral load measured in nasopharyngeal swab by Cycle Threshold at 0, 24, 48, and 72 hours after initiation of core warming
2. Duration of mechanical ventilation
3. Patient mortality

7.2 Sample Size and Power Determination

Based on a prior study in patients with sepsis, a maximum temperature of 38.3°C to 39.4°C was associated with survival (aHR 0.61 [95% CI, 0.39-0.99]).[29] However, the effect of warming specific to COVID-19 patients remains uncertain, and as such, we are unable to accurately perform a power calculation for this pilot study. We believe that a total of 10 patients for each group will be required to yield the necessary pilot data to make an appropriate conclusion regarding the potential utility of core warming in reducing viral shedding, improving pulmonary physiology, reducing mechanical ventilation duration, and increasing patient survival. It is anticipated that data from this pilot study can be used for planning future larger studies.

7.3 Statistical Methods

We will utilize standard measures to report outcomes and measure differences between groups. Specifically, we will use descriptive statistics, including mean (standard deviation) and median (interquartile range). Normality will be assessed using histograms and the Kolmogorov–Smirnov test. Categorical variables will be compared using the chi-squared test or Fisher exact test. Continuous variables will be compared using the independent samples t or Mann–Whitney U test.

7.3.1 Efficacy Analysis

This is a pilot study to determine the potential role of core warming during COVID-19 treatment..

7.3.2 Interim Safety Analysis

All subjects entered into the study and randomized at the baseline timepoint will have detailed information collected on adverse events for the overall study safety analysis. An interim safety analysis will be performed after the first 10 subjects are enrolled in the trial. At this time the safety and tolerability of the study device will be assessed and if deemed safe and appropriate, enrollment will continue to 22 subjects.

7.4 Subject Population(s) for Analysis

All patients enrolled, randomized to a study arm, and completed in the study will be included for analysis.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:

Unanticipated adverse device effect is any serious adverse effect on health or safety, any 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

8.1.3 Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.1.4 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1.5 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.1.6 Post-study Adverse Event

All unresolved adverse events considered probably or definitely related should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.1.7 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for additional surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event case report form (CRF). All clearly related signs, symptoms, and clinically significant abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period (consent through 30 day follow up) will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Classification of Adverse Events

Severity

- **Grade 1**: **mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.
- **Grade 2**: **moderate**; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- **Grade 3**: **severe** or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4**: **life-threatening** consequences; urgent intervention is indicated.
- **Grade 5**: **death** due to an AE.

Relatedness

1) **Definite:** the AE is clearly related to the research procedures
2) **Probably:** the AE is likely related to the research procedures
3) **Possible:** the AE may be related to the research procedures
4) **Unlikely:** the AE is doubtfully related to the research procedures
5) **Unrelated:** the AE is clearly not related to the research procedures

Expectedness

AEs must be assessed as to whether they were expected to occur or were unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label.

Expected: an AE known to be associated with the intervention or condition under study.

OHRP defines an unexpected AE as any AE occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and b) other relevant sources of information, such as product labeling and package inserts; or

2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

8.4 Adverse Event Reporting Period

For this study 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 (1-Month follow up visit/Visit3). Adverse events that do not require expedited reporting (see section 9.5 below) will be reported in summary to the IRB at continuing review.

8.5 Expedited Reporting of Events

Any study-related unanticipated problem posing risk to subjects or others, and any type of unanticipated serious adverse event or unanticipated adverse device effect, will be reported to the IRB in accordance with the institutional and FDA requirements. Investigators will use the appropriate SAE/UP CRF to record events and a line item will also be added to the AE log CRF.

The minimum necessary information to be provided at the time of the initial expedited event report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

8.5.1 Follow-up report

If an SAE, UP or Unanticipated Adverse Device Effect has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all events are followed until either resolved or stable.

8.5.2 Sponsor reporting: Notifying the Funding Sponsor

Electronic notification of any adverse events related to the use of the core warming device will be sent to the funding sponsor as determined by the principal investigator and study team.

8.6 Unblinding Procedures

The study team will not be blinded to the randomization assignment. The study team will be instructed to maintain blinding for participants unless a participant has a clinical need to know their randomization assignment. The decision to unblind will be at the discretion of the study PIs and only if unblinding would change clinical care. Unblinding for safety reasons will be recorded in study records and it will be reported to the IRB and the funding sponsor at the time of continuing review.

8.7 Data and Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. The Principal Investigator and designated members of the study team will be responsible for monitoring subject safety and applicable reporting to the IRB and study sponsor. This safety monitoring will include careful assessment of eligibility and detailed assessment and appropriate reporting of adverse events as noted above. Data collected on the study will be reviewed after 10 people are enrolled in the study. Another data review will occur at 22 patients enrolled.

9 Study Administration, Data Handling and Record Keeping

9.1 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.

9.2 Data Collection and Management

Data will be collected by trained research staff using source documents and CRFs. Source and CRFs will be entered into a RedCap data management system. Participants will be assigned a Participant ID “PID” for use on CRF data collection for entry into the data management system 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 case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. The study data will be stored indefinitely. A de-identified data set may be shared with the funding sponsor.

9.3 Records Retention

Study records, including administrative and participant related source and CRFs, will be retained for 7 years after the completion of the research (often marked by a final progress report).

10 Study Monitoring, Auditing, and Inspecting

10.1 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. ICU), and has adequate space to conduct the monitoring visit.

10.2 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.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the funding sponsor before commencement of this study if required. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate or legally authorized representative, and the appropriately delegated research staff obtaining the consent.

11.1 Risks

Risks of the study procedures are described below:

Core warming risks: Placement of the core warming device, similar to any device in the esophagus, can result in or exacerbate esophageal tissue damage, particularly in patients with known esophageal deformity or evidence of esophageal trauma. These risks are similar to those who receive the standard of care orogastric or nasogastric tubes inserted into the esophagus during routine clinical care of ICU patients.

There is also a risk that placement of the core warming device may result in movement of the tongue to the side, which can persist after removal; however, it is unclear whether this tongue deviation is caused by the endotracheal tube used during mechanical ventilation or if it is part of the disease progression of COVID-19 infection. Tongue deviation is one of the known sequelae of infection with SARS-CoV-2, better known as COVID-19.[53][54][55] Electromyography of the muscles innervated by the pharyngeal, superior laryngeal, and recurrent laryngeal branches of the vagus nerve, and by the accessory and hypoglossal nerves, have shown asymmetric patterns of acute or chronic neurogenic damage, or both.[54] Whether these findings reflect the direct (viral) or indirect (immune-mediated) effect of SARS-CoV-2 remains to be established.[54]

Loss of Confidentiality Risks: There is the potential for loss of confidentiality during data collection.

Temperature modulation risks: Warming critically ill septic patients has been previously investigated, with no unforeseen risks identified. Whole-body hyperthermia (to core body temperatures > 39.0°C) has been tested in sedated patients undergoing colorectal surgery, as well as in oncological patients in combination with radiotherapy and/or chemotherapy.[52] Patients in these studies suffered no serious hyperthermia-related side effects despite being warmed to temperatures much higher than targeted in this study.

Potential adverse effects of external warming/body temperature elevation include:
(1) Vasodilation of arteriovenous shunts in the skin resulting in decreased blood pressure and an increase in vasopressor dose
(2) Elevated heart rate
(3) Increased respiratory rate
(4) Increased metabolic rate
(5) Patient discomfort
(6) Sweating
(7) Worsened long-term neurological function in patients with acute stroke or post-cardiac arrest
(8) Exacerbation of multiple sclerosis symptoms

This study will only enroll COVID-19 patients, and will exclude any with acute stroke, post-cardiac arrest, or multiple sclerosis.

11.2 Benefits

There are no known direct benefits to the participants in this study. There may be a benefit to core warming of patients with COVID-19. The knowledge gained by participation in this study may benefit society as a whole in the future and potentially lead to additional studies.

11.3 Risk Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study.

11.4 Informed Consent Process/ HIPAA Authorization

Participants' surrogate or legally authorized representative will be provided an IRB approved consent form describing this study and providing sufficient information to make an informed decision about their participation in this study. A verbal review of the consent form will take place with the participant and delegated personnel. This consent form will include HIPAA authorization language which will also be reviewed with the participant. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate or legally authorized representative, and the investigator-designated research professional obtaining the consent. The participant will be consented in a private clinical space and will be given ample time to ask questions and have questions answered. As the majority of the procedures that will occur are standard of care, we will clearly discuss what the research part of the day and days after will include. The voluntary nature of the study will be reviewed and participants will be told that should they choose not to consent, their clinical care will not be effected.

12 Study Finances

12.1 Funding Source

Pending

12.2 Conflict of Interest

All Investigators will follow the institution's policies on Conflicts of Interest related to research.

12.3 Participant Stipends or Payments

Participants will not receive payment.

13 Publication Plan

Investigators will follow all applicable policies and guidelines relating to publishing study results. The research team will share materials planned for publication to the Funding Sponsor according to the terms of the Clinical Trial Agreement.

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