Pilot Randomized Clinical Trial of Therapeutic Hypothermia Plus Neuromuscular Blockade vs. Standard of Care in Patients With Moderate to Severe ARDS - the Cooling to Help Injured Lungs (CHILL) Pilot Study

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Study Protocol 1.0

Date: May 6, 2020

CHILL-pilot:
Cooling to Help Injured Lungs
Pilot Study

Manual of Operations

May 6, 2020

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1/ Study Overview

1.1/ Study Synopsis

There is both a rational theoretical basis and empiric preclinical and clinical data to support using therapeutic hypothermia (TH) as a new treatment modality for ARDS. Since the reduction in metabolism by TH plus neuromuscular blockade (NMB) to block shivering reduces the requirement for pulmonary gas exchange [1], TH+NMB will reduce exposure of vulnerable lung parenchyma to injurious mechanical ventilation as does low tidal volume ventilation and prone positioning. However, TH also directly dampen two cell signaling pathways that contribute to lung injury, Transient Receptor Potential Cation Channel Subfamily V Member 4 (TRPV4) [2] and p38 Mitogen-activated kinase (MAPK) [3]. The additional effects of TH on pathogenic cell signaling suggests it will confer lung protection in ARDS that is additive with current therapies. Preclinical studies demonstrate that hyperthermia worsens [4-9] and hypothermia mitigates [10-22] animal models of ALI through effects on leukocytes and lung endothelium and epithelium [8,9,23-25]. Clinical studies of temperature management in ARDS is still at an early stage, but an older small prospective non-randomized controlled trial of TH (33.7±0.6°C for 70±15h) in moribund patients with septic shock and ARDS showed improved survival in the TH group (3 of 9 vs. 0 of 10) [26]. This study preceded modern definitions and management for ARDS and mortality rates in both groups were much higher than current experience. A trial of TH (35°C) vs. normothermia in 31 patients with renal transplant and respiratory failure due to infection showed improved patient and renal graft survival in the TH group [27], but no measures of lung function were included. Our CHILL historical-controlled open-label study of TH+NMB in patients with ARDS showed TH+NMB to be safe and to improve mortality and 28-day ventilator-free days (VFDs) compared with historical controls. Although these studies were not randomized control trial (RCT), they provide strong support for our hypothesis that TH+NMB will be lung-protective in ARDS. There is additional justification for TH in COVID-19. The early autopsy studies have shown pathophysiology that looks like ARDS. Many of the cytokines released during the cytokine storm associated with severe COVID-19 pneumonia and ARDS are reduced at clinically relevant hypothermic temperatures.

We have been approved for funding by Department of Defense (DoD) to support for a 4-year multicenter RCT of TH+NMB for 48h vs. standard of care with contract to be completed June 1, 2020 and with enrollment to begin in Fall of 2020. This study was designed prior to the onset of COVID-19, which is now the most common cause of ARDS and will likely continue to be in the Fall, 2020 and perhaps beyond. Therefore, it is important to decide whether patients with COVID-19 ARDS should be enrolled in our CHILL trial. Therefore, we will conduct a 20-patient pilot safety and feasibility trial of our CHILL TH+NMB treatment vs. control in COVID-19 patients with ARDS who meet the inclusion/exclusion criteria of our DoD-funded trial. The major objective of the proposed pilot trial is to determine whether it is safe and feasible to include patients with COVID-19 ARDS in our Phase IIb CHILL RCT of TH+NMB vs. control in patients with moderate to severe ARDS.

The pilot will be conducted at the University of Maryland Medical Center. To facilitate randomization within the inclusion window, we will consent and enroll based on partial fulfillment of randomization criteria and randomize once all criteria are met. Patients will be

eligible for enrollment when they have been diagnosed with COVID-19 by PCR, and have met all Berlin criteria for moderate to severe ARDS within the 48h inclusion window except the P/F ratio ≤200 but will not be randomized until P/F ratio (measured or imputed based on SpO_2) is ≤200 (while on ≥8 cm H_2O PEEP and ≥0.6 FiO_2). We plan to randomize a total 20 patients over 4 months to hypothermia (core temperature 34°-35°C for 48h) plus NMB or usual temperature management. The primary outcome measures will be effectiveness of cooling in achieving and maintaining the target temperature and safety measures. Secondary outcomes will include 28-day ventilator-free days (VFDs), 28-day ICU-free days, oxygen saturation index (OSI), driving pressure, Sequential Organ Failure Assessment (SOFA) score, 60-day and 90-day survival, 90-day functional assessment, cognitive assessment at ICU and hospital discharge, and biomarkers of inflammation and lung injury. Since the nature of the intervention precludes blinding, all treatment and clinical decision making related to study outcomes will be protocolized and compliance with study protocols will be monitored.

1.2/ Study Aims and Objectives

We will conduct the CHILL-pilot single-center RCT of TH in patients with COVID-19 and ARDS with P/F<250 to address the following specific aims:

1. ***Aim 1: Analyze the safety and feasibility and the potential lung protective effect of treating patients with COVID-19 infection and ARDS with P/F < 200 with mild TH (core temperature 34°-35°C) + NMB for 48h compared with controls receiving standard temperature management.*** We expect the TH-treated group to achieve targeted temperature within 4h of randomization and to maintain TH for 48h without significant increase in serious adverse effects compared with the control arm.
2. ***Analyze the potential lung protective effect of mild TH (core temperature 34°-35°C for 48h) and NMB in patients with ARDS and P/F < 200 compared with controls receiving standard temperature management.*** We expect the TH-treated group to trend toward having more 28-day VFDs (primary) and 28-day ICU-FDs, and improved day-3 driving pressure and OSI than the controls.
3. ***Evaluate the effects of TH on systemic inflammation and extrapulmonary organ dysfunction.*** We expect the treated group to have reduced levels of proinflammatory mediators and lower Sequential Organ Failure (SOFA) scores than controls.

The proposed pilot study will determine whether we can safely include patients with COVID-19 and ARDS in our larger Phase IIb trial of TH and NMB in patients with ARDS. It will help us determine whether the 48h duration of cooling is sufficient.

1.3/ Background and Rationale

A substantial body of literature suggests that fever may worsen and hypothermia may mitigate ALI. Prior studies show that exposure to febrile-range hyperthermia (FRH) impairs endothelial barrier function, increases leukocyte transendothelial migration potential, and increases epithelial cytokine expression and apoptosis in cell culture, and worsens lung injury in animal models induced by LPS instillation, bacterial pneumonia, hyperoxia, and mechanical ventilation. In our reanalysis of core temperature and outcomes in the ICAP database, 65% of ARDS patients

had fever within the first 3 days of developing ARDS and the presence of fever reduced the likelihood of ventilator liberation within 24h by 33%. Hypothermia was lung protective compared with normothermia in animal models of ALI induced by intratracheal LPS, paraquat, hemorrhagic shock, mechanical ventilation, pneumococcal pneumonia, and air embolism. The Villar and Slutsky non-randomized concurrently controlled trial of TH in patients with septic shock and ARDS also showed a modest increase in PaO2/PAO2 ratio (0.19±0.04 vs. 0.15±0.04) in the hypothermic group. A recent small retrospective review of cardiac arrest cases showed that treatment with a standard TH protocol (core temperature 32°-34°C) tended to improve pulmonary function. Studies from our laboratory and others suggest that signaling events that cause pulmonary vascular permeability, including MAPKs and the stretch-activated ion channel, TRPV4, are suppressed by clinically relevant hypothermia, providing potential mechanisms for lung-protective effects of hypothermia. These studies provide strong support for our hypothesis that TH will benefit patients with ARDS. Because the lung pathology in COVID-19 shows many of the same features as ARDS from other causes, because of the positive results we have had in treating patients with influenza-associated ARDS, and because many of the cytokines shown to be associated with severe COVID-19 disease exhibit temperature-dependent expression, we expect that our TH+NMB protocol will be safe, feasable, and beneficial in patients with COVID-19 ARDS.

1.4/ Abbreviations and Acryonyms

COVID-19: Corona virus disease-2019

CHILL: Cooling to Help Injured Lungs

ALI: Acute lung injury

TH: Therapeutic hypothermia

NMB: Neuromuscular blockade

ARDS: Acute respiratory distress syndrome

SOFA: Sequential organ failure assessment

VFDs: Ventilator-free days

P/F: Ratio of partial pressure of oxygen:fractional index of inhaled oxygen

OSI: Oxygen saturation index

ECMO: Extracorporeal membrane oxygenation

FRH: Febrile-range hyperthermia

MICU: Medical intensive care unit

UMMC: University of Maryland Medical Center

CRRT: Continuous renal replacement therapy

SAE: Serious adverse event

HSCTI: Human subject clinical trial information

LAR: Legally authorized representative

CRF: case report forms

CCU: Cardiac care unit

CCRU: Critical care receiving unit

CVP: Central venous pressure

CCC: Clinical Coordinating Center

DCC: Data Coordinating Center

CSPCC: Cooperative Studies Program Coordinating Center (in Perry Point, MD)

2/ Study Organization and Staff Roles and Responsibilities

2.1/ Participating Centers

2.1.1 Study Center

University of Maryland Medical Center (Downtown campus)

2.1.1.1 Study Units

UMMC Medical Intensive Care Unit (MICU)
UMMC Trauma 6S/BCU/Critical Care Resuscitation Unit (T6S/CCRU)
UMMC 10W

2.1.1.2 Clinical Operations Core (CC)

The Clinical Operations Core (CC) will be headed by Drs. Jeffrey Hasday and Carl Shanholtz
The CC is responsible for oversight of all aspects of trial enrollment and recruitment, from feasibility assessment, to planning, tracking and, if necessary, improving protocols. The CC is also responsible for supervising the biomarker analysis.

2.1.1.2.1 Specific Responsibilities of the CC:

1. Collect and maintain all regulatory documents (curricula vitae, CITI GCP certifications, CITI human subjects research, clinical lab CLIA certification and normal ranges).
2. Provide training to all clinical personnel regarding GCP, screening and clinical protocols.
3. Develop and maintain all study protocols and standard operating procedures regarding patient screening and clinical protocols and collecting and handling research samples.
4. Maintain real-time tracking and correction of clinical protocol noncompliance
5. Establish and manage the IRB approval
6. Report adverse events to IRB, DC, and DSMB
7. Maintain continuous monitoring of data quality
8. Monitor human subject protection
9. Manage the CHILL-pilot record in Clinicaltrials.gov
10. Monitor enrollment for meeting timing and budgetary milestones
11. Maintain oversight of biomarker core
12. Manage supply of Nimbex provided as a study drug gift by Abbvie Pharmaceutical

2.1.2 Data Management

2.1.2.1 Data Management and Analysis Core (DC)

The Data Management and Analysis Core (DC) will be jointly run by Clayton Brown, PhD, and Michael Terrin, MD, CM, MPH. The DC is responsible for oversight of randomization and data management, data quality, statistical analysis, and providing data summaries to external groups.

2.1.2.1.1 Specific Responsibilities of the DC:

1. Maintain oversight of the Randomization and Data Management Core, including the computer-based CHILL treatment assignment tool and Screening/enrollment tool.

2. Provide instruction and training to clinical personnel regarding randomization and data management processes, procedures, and metrics.
3. Perform database back-up and post-study database lock.

2.1.3 Laboratories

2.1.3.1 The Biomarker Core (BC)

The Biomarker Core will be directed by Jeffrey Hasday, MD

2.1.3.1.1 Biomarker Core Components

The Core has three components:

1 sample storage
2 University of Maryland Cytokine Core Laboratory
3 Dr. Hasday's basic research laboratory.

2.1.3.1.2 Biomarker Core Procedures

1. Samples will be stored in a remotely monitored -80°C freezer with liquid CO2 back-up located in the University of Maryland Baltimore Health Science Facility-II in ancillary space adjacent to Dr. Hasday's basic research laboratory (Rm S116).
2. Labeled EDTA-anticoagulated blood samples from all participating ICUs will be transported on ice directly to Dr. Hasday's laboratory within 30 minutes of collection and processed as described in the Sample and Processing section. The Hasday laboratory is adjacent to UMMC
3. Samples will be batched for assays to be performed every 4-6 months. Dr. Hasday, will hand-carry one aliquot in labeled cryotubes per blood draw in marked freezer boxes on ice to the Cytokine Core Laboratory located on the seventh floor of the adjacent Bressler Research Building.
4. Samples will be received by Ms. Lisa Hester, Supervisor of the Cytokine Core Laboratory, who will place the samples in the Cytokine Core Laboratory remotely-monitored, liquid-CO2-backed-up -80°C freezer until she performs the planned immunologic assays.
5. All assays will be performed in the Cytokine Core Laboratory using in-house ELISAs (IL-1ß, IL-6, IL-8, IL-18, and sTNFR1) or purchased ELISA kits (sRAGE, SP-D, sICAM-1, MMP8).
6. Dr. Hasday is the Director of the University of Maryland Cytokine Core Laboratory and has weekly meetings with Ms. Hester to review throughput and quality of all projects in the Cytokine Core Laboratory. The progress of the CHILL-pilot analysis will be discussed as part of these weekly meetings.
7. Dr. Hasday will analyze all CHILL-pilot biomarker data for reproducibility and monitor performance of all biomarker assays by inspecting the standard curve, monitoring within-assay coefficient of variance between replicate measurements, and between-assay coefficient of variance based on pre-aliquoted internal controls to be included on each assay plate.

2.2/ Administration and Governance

2.2.1 Committees

2.2.1.1 CHILL Pilot Executive Committee (CEC)

The CEC membership will include Drs. Hasday, Shanholtz, Terrin, and Brown. The CEC will meet bi-weekly to monitor progress with study planning milestones during the preparation phase and enrollment, randomization, retention, and data quality milestones during the enrollment and randomization phase. The CEC will review suggestions for protocol amendments from all CHILL-pilot personnel and make final decisions about modifying protocols. Dr. Terrin will prepare reports for Data Safety Monitoring (DSM) meetings with input from Dr. Brown.

2.2.1.1.1 Responsibilities of the CEC:

1. The CEC will meet bi-weekly to monitor progress with enrollment, randomization, retention, and data quality milestones and re-evaluate and revise as needed all study protocols.
2. The CEC will review suggestions for protocol amendments from all CHILL-pilot personnel and make final decisions about modifying protocols.
3. Dr. Terrin will prepare reports for DSM meetings with input from Dr. Brown.
4. Serious/Reportable Adverse Event (SAE/RAE) Adjudication and Reporting: The following is an initial plan for adverse event (AE) reporting (the plan will be revised by the CHILL leadership with input from CHILL personnel and the CHILL Data Safety monitor, Dr. Verceles, based on experience with the ongoing study). Serious Adverse Events are defined as any deaths, life-threatening events, or events that prolong hospitalization that occur within the first three study days (which includes the period of cooling and rewarming in the Therapeutic Hypothermia arm). All SAEs will be reviewed by Dr. Hasday based on information provided by Dr. Shanholtz. Dr. Hasday will report the SAE, including his assessment of relatedness to study procedures, to the UMB IRB and the Data and Safety Monitor, Dr. Avelino Verceles within 48 hours of discovery. Reportable AEs (RAEs) that do not meet the threshold for SAEs are defined as any clinically important untoward medical occurrence in the first study week which is different from what is expected in the clinical course of a patient with ARDS. All other AEs will be tabulated without case-by-case review unless a difference between treatment groups calls for review of a group of cases. Dr. Terrin will submit monthly tabular reports of all SAEs/RAEs to Dr. Verceles and will submit tabular summaries of all AEs to Dr. Verceles every 6 months. The AE summary will be included in the bi-annual review by Dr. Verceles.
5. Ongoing Scientific Review: CEC members and any other interested CHILL-pilot personnel may bring new information with potential impact on study protocols and analysis to the attention of the entire CEC. The topic will be added to the CEC meeting agenda and background information distributed with enough lead time to allow a productive discussion.
6. Processing Requests for Sample Sharing: Dr. Hasday will provide to the CEC all information about sample sharing requests and information about sample availability

and status of the CHILL-pilot biomarker analysis to inform decisions by the CEC about the priority of sample sharing requests.

7. Publication Preparation: The entire CEC membership will participate in manuscript writing. Drs. Terrin and Shanholtz will take the lead with the first paper about study design. Drs. Hasday and Brown will take the lead the manuscript reporting the main study results. Dr. Hasday will update the Clinicaltrials.gov record.
8. Oversight of Biomarker Core: The research biomarker analysis will be performed by the CHILL-pilot Biomarker Core with oversight by Dr. Hasday.

2.2.1.2 Data Management Core Committee

Oversight for the Randomization and Data Management Core will reside within the DC. One or members of the clinical team will transcribe data from the patient study binder to an Excel form that summarizes the salient data for analysis to be performed by Drs. Clayton Brown and Michael Terrin. Dr. Brown will oversee generation of random assignments into the computer-based CHILL assignment tool, which records date and time, and name of investigator performing randomization.

2.2.1.2.1 Responsibilities of the Data Management Core Committee

1. During the self-funded phase Dr. Brown will provide the following two monthly recruitment reports:

   (1) a screening/recruitment report that presents the counts of patients screened, enrolled, and randomized without treatment assignment information, for distribution to and discussion in the CEC, and

   (2) a list of patient ID (PID) numbers and letter codes (Letcode) sorted by date of randomization with treatment stratum and treatment assignment for each patient. Drs. Terrin and Brown will check the list against the randomization schedules prepared by Dr. Brown, against the monthly screening and randomization table and use it to ensure congruence with clinical site documents and in preparation of DSM reports with tabulated data.

2.2.2 Funding Agency

The initial phase of this pilot RCT is self-funded. The larger Phase IIb trial is funded by DoD with enrollment to begin Fall, 2020

2.2.3 Data Safety Monitoring (DSM)

2.2.3.1 DSM composition

2.2.3.1.1 For CHILL-pilot: self-funded phase

The Data Safety Monitor for the self-funded phase is Dr. Avelino Verceles, a Pulmonary and Critical Care Physician who is not directly related with the study, is familiar with the management of ARDS and the conduct of clinical trials, and who has been approved by the University of Maryland Internal Review Board.

2.2.3.2 DSM procedures

The Data Analysis and Management Core (DC) will be responsible for managing Data Safety Monitoring, including preparing reports for bi-annual review by Dr. Verceles. The following is an initial plan for adverse event (AE) reporting, which will be modified and finalized based on discussions with the DSMB:

1. Clinical site staff will be responsible for recording all AEs on the appropriate CRF.
2. Any deaths, life-threatening events, or events that occur within the first three study days, including NMB, cooling and rewarming, and unexpected SAEs occurring in the first study week will be reviewed by Dr. Hasday based on information provided by Dr. Shanholtz.
3. Dr. Hasday will report the SAE, including his assessment of relatedness to study procedures, to the University of Maryland Baltimore IRB and Dr. Verceles within 48 hours of discovery.
4. All other AEs will be tabulated without case-by-case review unless a difference between treatment groups calls for review of a group of cases.
5. Dr. Terrin will submit monthly tabular reports of all SAEs and other RAEs to Dr. Verceles and will submit tabular summaries of all AEs to Dr. Verceles every 6 months.
6. Since this is a small pilot study, there are no plans for an interim analysis and early termination based on futility or proven benefit.

2.3/ Roles and Responsibilities

2.3.1 Multiple Principal Investigators (MPI)

2.3.1.1 Contact MPI

The contact MPI for the CHILL-pilot is Jeffrey Hasday, MD. Responsibilities include:

1. Dr. Hasday will direct the CHILL-pilot Administration Group
2. Dr. Hasday will chair the CHILL-pilot Executive Committee (CEC).
3. Dr. Hasday will interact with Ms. Christina Riggs regarding distribution of study resources, including quarterly payments to UMMC for study-related costs and to Axio Research LLC should an R24 grant be awarded.
4. Dr. Hasday will direct the Biomarker Core and ensure proper handling of research samples and timely, high quality biomarker analysis.

2.3.1.2 MPI for CC

Dr. Shanholtz is Leader of the Clinical Operations Group. Responsibilities include:

1. Dr. Shanholtz will interact with the CHILL-pilot study coordinator, Jennifer McGrain, to:
    a. oversee efficient operation of the Participating ICUs, and to
    b. ensure that all members of the Chill-pilot Clinical Team (e.g. Pulmonary and Critical Care fellows; cross-covering coordinators) are appropriately trained in CHILL-pilot study protocols.
2. Will adjudicate AEs and SAEs with Dr. Hasday and assist in preparing reports for the DSMB

2.3.1.3 MPI for DC

The MPIs for the Data Management and Analysis Core (DC) are Michael Terrin, MD, CM, MPH and Clayton Brown, PhD. Responsibilities include:

1. Dr. Terrin will oversee activities of the DC, including the Biostatistics and Data Management Group
2. Dr. Brown will lead the Biostatistics and Data Management Group.
3. Dr. Brown will be responsible for designing and executing all statistical analyses.
4. DC offices are collocated in Howard Hall near Ms. Andrea Lefever, CHILL-pilot Clinical Research Specialist.
5. Under Dr. Terrin's direction, Ms. Lefever will produce CHILL-pilot Data and Safety Monitoring reports for Dr. Verceles
6. DC's physical and administrative separation from the CC is an essential part of the CC/DC "firewall."

2.3.2 Coinvestigators

Coinvestigators from within the Division of Pulmonary and Critical Care Medicine (PCCM) and outside the division will have the following responsibilities:

1. Maintaining education and study procedure competency in their respective units
2. Assisting in the screening and enrollment of study participants from the participating units.
3. Assisting in obtaining informed consent.
4. Interpretation of clinical data (medical history, physiologic, laboratory, and radiographic) related to all study procedures (screening, enrollment, data recording, AE/SAE reporting).
5. Order-writing and implementation of study procedures
6. Being available to unit staff for study-related questions
7. Identification of protocol deviations and other reportable events and their correction
8. Identification of AEs/SAEs and assisting in their reporting
9. Assisting in obtaining and handling of biological specimens

2.3.3 Coordinators

Ms. Thelma Harrington, RRT, MBA is the lead study coordinator and will oversee a coordinator team that includes Olga Kolesnik and a team of pulmonary and critical care fellows. Responsibilities include:

1. Preparing and maintaining regulatory documents
2. Screening, enrollment, and randomization in all study units
3. Obtaining informed consent from participant or their legally authorized representatives (LAR).
4. Completion of case report forms (CRFs)
5. Identification of protocol deviations and their correction
6. Identification of AEs/SAEs and reporting
7. Obtaining and handling of biological specimens
8. Preparing data summaries for analysis

9. Preparing reports for the DC, DSMB, and the IRB

2.3.4 Other

3/ Participant Recruitment

3.1/ Screening

All patients 18-65 years old in one of the study ICUs with a confirmed diagnosis of COVID-19 within the last 3 weeks and on mechanical ventilation less than or equal to 7 days will be screened using the On-line Screening Log, which assigns the 3-digit Study ID and 3-letter patient identifier and stores the patients' demographic information, final status (enrolled or excluded) and, if applicable the reason.

Checking/updating patient census:

1. In Epic, under lists, click on a list called "CHILL Screening." You will see all patients in the MICU and CCRU (T6S BCU) with information required for CHILL screening.
2. Go to "Screener Signout sheet" tab.
3. Put in date and time and your name (from pulldown menu).
4. Update census by adding new names and deleting those patients who were discharged/transferred from the unit. Put in patient study status from Pulldown menu. "Never eligible" means that the patient is out of the age inclusion criteria or has been ventilated for > 7 days. "Not eligible" means not currently eligible but could be in future (not yet on mechanical ventilation).
5. Check those patients who were "not eligible" at the previous screen (you can ignore the patients who are "never eligible").

Initial Patient Data Entry using on ling screening tool:

1. Go to Microsoft 365 and log in using UMB sign on information, then open One Drive. You should see a few Excel programs. There is a COVID_CHILL_Assignment tool and a CHILL_COVID_Online_Screening tool as well as Demo versions of each (to practice with).
2. Select "CHILL_COVID_Online_Screening_Log_1.0," click on the 3 vertical dots next to the file title, select "Open" and then on "Open in app." If opening on a Mac, you will be given the option to enable macros. On a PC, you will have to manually enable macros once the file is open using the following steps:
    a. Once the file is open, click on the "File" tab
    b. Click on the "Enable Content" icon (upper left)
    c. Click on "Advanced Options"
    d. Select "Enable Content for this Session."
    e. The programs should the work.
3. Go to "Sheet1" tab.
4. To enter a new patient and obtain a 3-digit study number and a 3-letter patient identifier, first ensure that the patient has not been previously screened by clicking on Sheet 1 and using the Excel find tool to check for the patient's MRN number.
5. If the patient has not been previously screened, click on "Sheet2" tab.
6. Push the "Push to Start" button. All cells should empty

7. Enter your name from the pulldown menu, the Patients name (Last, first), MRN number, Medical Unit (from the pulldown menu) and room number where they are currently located or are being immediately being transferred to.
8. If you know whether they are enrolled or excluded at this time, you can add this from the pulldown menu. If excluded indicate the reason from the pulldown menu. If multiple reasons, select "multiple exclusions" from the end of the pulldown menu. If you do not know the final status at this time, you can add it later. If you leave a required field empty the program will let you know.
9. Push the "Push button for study number and ID" button. The 3-digit number and 3-letter patient identifier are indicated in cells B14 and B15. Record them on the Screening/Enrollment/Randomization CRF. All data and date/time stamped are recorded on Sheet 1.
10. All data are automatically saved and the sheet locked so you just have to click on the close button.

Subsequent Entry of Final Status:

1. If you did not enter the final status when first obtaining patient study ID number and 3-letter identifier, click the "Push to Start" button on Sheet 2.
2. Enter the patient 3-digit study number and 3-letter patient identifier in cells B21 and C21. Make sure the 3-letter identifier is in ALL CAPS. If you don't have immediate access to the number/letter ID, you can find them on Sheet 1.
3. Enter the Final Status and Reason for Exclusion if applicable from the pulldown menus. If multiple exclusions, select "multiple exclusions" from the end of the pulldown menu.
4. Push the "Push button to enter final status" button.
5. If the number and 3-letter ID match, you will get a message that the information has been added; otherwise you will get a message that there is a mismatch. In this case, check the number and letters and make sure letters are in ALL CAPS and push the button again.
6. All data are automatically saved and the sheet locked so you just have to click on the close button.

If you make a mistake with data entry on sheet 1, make sure you use the correct patient number/3-letter code in the sequence and let me know so I can fix any errors (e.g double entry).

3.2/ Enrollment

3.2.1 Inclusion Criteria

1. COVID-19 diagnosed by PCR within 3 weeks
2. men and women
3. any race/ethnicity
4. 18-65 years of age
5. endotracheal tube or tracheostomy in place and mechanically ventilated for < 7 days;

6. radiologic evidence of bilateral pulmonary infiltrates not fully explained by hydrostatic pulmonary edema
7. access to an LAR to provide consent (remote consent is permissible).

3.2.2 Exclusion Criteria

1. Missed ARDS window (>48hrs)
2. Missed mechanical ventilation window (>7 days)
3. Refractory hypotension (> 0.2 mcg/kg/min of norepinephrine or equivalent dose for minimum of 6 h)
4. Core temperature <35.5°C while not receiving CRRT
5. Patient is unable to give consent and no legally authorized representative is available;
6. Significant, active bleeding (>3u blood products and/or surgical/IR intervention)
7. Platelets <10K/mm^3 (uncorrected)
8. Active hematologic malignancy
9. Skin process precludes cooling device
10. Moribund, not likely to survive 72h
11. Pre-morbid condition makes it unlikely that patient will survive 28 days
12. Do Not Resuscitate status
13. Not likely to remain intubated for ≥48h
14. Physician unwilling to participate
15. Severe underlying lung disease
    a. On home O_2
    b. On BIPAP (except for OSA)
    c. Prior lung transplantation
16. BMI >45 kg/m^2
17. Known NYHA class IV heart disease
18. Acute Coronary Syndrome past 30 days (MI, unstable angina)
19. Cardiac arrest within 30 days of enrollment
20. burns over >20% of the body surface
21. severe chronic liver disease (Child-Pugh of 12-15)
22. Previously randomized in CHILL study

3.3/ Randomization

Subjects will be stratified by proning status at enrollment and randomized within each stratum to receive TH or usual temperature management using a 1:1 assignment ratio. Treatment group assignment will be made using an Excel-based assignment tool stored on the UMB Microsoft OneDrive, which records date, time, and investigator who makes the treatment assignment. Baseline APACHE II, Sequential Organ Failure (SOFA) score 3, driving pressure, P/F ratio, and oxygen saturation index will be documented at time of randomization to assess comparability of disease acuity between groups.

3.3.1 Inclusion Criteria for Randomization

In addition to meeting all criteria for enrollment, subjects must meet the following criterion **at time of randomization**: have P/F <200 with PEEP ≥8 cm H2O within 48h of randomization and within 14 days onset of COVID-19 symptoms. Alternatively, if ABG values are not available, P/F ratio <200 with PEEP ≥8 cm H_2O; If ABG values are not available, the P/F ratio may be inferred from SpO2 values based on eTable 2 from Brown et al as long as following conditions are met:

a. SpO2 values are 80-96%
b. SpO2 is measured ≥10 min after any change in F_IO_2
c. PEEP is ≥ 8 cm H_2O
d. the pulse oximeter waveform tracing is adequate
e. the qualifying inferred P/F ratio is confirmed 1-6 hrs after the initial determination.

eTable 2: Imputed PF ratio (cells) for combinations of SpO_2 (rows) and FiO_2 (columns)

	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

3.3.2 Randomization Procedures

Randomization will be performed by a macro-driven Excel spreadsheet (CHILL_COVID_Assignment_Tool 1.0) stored on the UMB Microsoft OneDrive:

1. Select “CHILL_COVID_Assignment_Tool 1.0,” click on the 3 vertical dots next to the file title, select “Open” and then on “Open in app.” If opening on a Mac, you will be given the option to enable macros. On a PC, you will have to manually enable macros once the file is open using the following steps:
    a. Once the file is open, click on the “File” tab
    b. Click on the “Enable Content” icon (upper left)
    c. Click on “Advanced Options”
    d. Select “Enable Content for this Session.”
    e. The programs should the work.
2. On Sheet 1, Push “Push to Start” button
3. Enter your name from pulldown menu and push “Push to Start” button

4. Enter 3-digit study ID number from pulldown menu and push “Push to Start” button.
5. Re-enter 3-digit study ID number from pulldown menu and push “Push to Start” button.
6. If numbers do not match you will get an error message.
7. Otherwise enter 3-letter identifier and push “Push to Start” button.
8. Enter proning status from pulldown menu and push the “Confirm proning status, then push this button to get assignment” button.
9. The treatment assignment will be displayed in cell B12, all information will be entered along with date/time stamp on Sheet 2.
10. All data are automatically saved and the sheet locked so you just have to click on the close button.

If you make a mistake, make sure you the correct treatment assignment right away and let me know about the entry error so I can fix it. If you put in the wrong proning status, repeat with correct status and let me know so I can fix the error. If you entered wrong patient number or 3-letter code, use the treatment assignment provided and let me know so I can fix the error.

3.4/ Informed Consent

Patients found on screening to qualify for enrollment in CHILL-pilot and whose ICU provider agrees will be offered participation in CHILL-pilot. Because eligible patients will be seriously ill, on high levels of mechanical ventilation, and receiving sedation and possibly NMB, informed consent will be obtained from the patient’s LAR by Drs. Hasday or Shanholtz, the CHILL-pilot Study Coordinator, or other Clinical Team member. CHILL-pilot study personnel who are also responsible for the clinical care of a potential subject will not participate in the consent discussion to avoid undue pressure. The information provided in the consent will cover the elements listed in the 21 CFR Part 50.25 and be approved by the UMB IRB. This includes the investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks, discomforts, and benefits, and potential alternatives including not participating and right to withdraw without penalty. Study staff personnel will offer to answer any questions. Consent will be documented by LAR signature on the IRB approved consent form LAR. No study procedure will be done prior to obtaining signed informed consent. Once patients regain decision making capacity as assessed using an IRB-approved Capacity Assessment tool, informed consent for continuing participation in CHILL-pilot will be obtained by the Drs. Hasday or Shanholtz or a Clinical Team member.

If the patient does not have capacity to provide informed consent and the LAR cannot be present in the hospital, we will pursue informed consent remotely through one of the following modalities: (a) telephone; (b) email; (c) FAX.

1. Initial Contact: The LAR will be identified from the patient’s electronic record and contacted initially by telephone. The team member will call from a private location with access to a non-team member witness (for verbal consent). The team member will identify themselves, confirm that the person on the line is the LAR, and state that they are calling to discuss having the patient participate in a research study. They will then offer to provide information to the LAR verbally or by FAXing or emailing a copy of the consent form.

2. Verbal phone consent: If the LAR selects the verbal consent option, the team member will read the consent form over the phone. The LAR will then be given time to ask questions, including the option to do so with a follow up phone call. Once the LAR is ready to give consent, a witness who is not part of the study team will join the call, the LAR will be asked if they any further questions, and consent will be obtained. The team member obtaining consent and the witness will then sign and date on the signature page of the consent form, print the patient's name on the participant name line, and indicate that consent was obtained verbally by checking the appropriate boxes at the bottom of the signature page. They will complete the LAR affidavit, sign page 1, and write verbal consent on the LAR signature line on page 2 and the witness will sign page 1.

3. FAX option: If the LAR selects the FAX option, they will provide a secure FAX number and a time and contact phone number for the team member to call to discuss the study and answer questions. The team member will FAX the consent form and page 2 of the LAR affidavit to the FAX number provided. To minimize loss of confidentiality, the consent form will be sent to the LAR without the patient's name included. They will call the LAR back at the established time, confirm that the LAR received all pages of the consent form and that they are legible. They will then discuss the study and answer questions (referring to appropriate pages in the consent form) as described for verbal consent. If the LAR is then willing to give consent, they will be asked to enter the patient's name on the participant name line, sign and date on the LAR signature line of the signature page, complete and sign page 2 of the LAR affidavit, and FAX the signed signature page of the consent form and LAR affidavit page 2 back to a secure FAX number where the LAR will be waiting. Alternatively, the LAR will be given the option of taking a picture of the signed signature page with their cell phone and emailing it back to the team member.

4. Email option: If, after advised of the possible loss of confidentiality with email transmission of the consent form, the LAR selects the email option, they will be asked for an email address and a time and phone number for a follow-up discussion of the study. The team member will send an email with a pdf file of the consent form and page 2 of the LAR affidavit attached to the email address provided by the LAR. To minimize loss of confidentiality, the consent form will be sent to the LAR without the patient's name included. A follow-up phone call will be conducted as discussed for FAX consent. If the LAR is then willing to give consent, they will be asked to print out the signature page of the consent form, enter the patient's name on the participant name line, sign and date on the LAR signature line, complete and sign page 2 of the LAE affidavit, take a picture of the signed consent form signature page and LAR page 2 with their cell phone, and email it back to the team member. Alternatively, the LAR will be given the option of FAXing the signed signature page back to the team member.

For emailed consent, the team member will print a hard copy of the emailed images. For the FAXed and email hardcopies, the team member will confirm that the patient's name is legibly recorded on the participant's signature line, sign and date on the Investigator signature line, and note how the consent was obtained by checking the appropriate boxes on the consent form. They will complete page 1 of the LAR affidavit and confirm that page 2 is adequately completed.

Electronic images of the signed signature page of the consent form and the LAR affadavit will be placed in the electronic medical record.

3.5/ Retention Strategies

We anticipate that most participating subjects will remain hospitalized, likely in the ICU, through study day 7 and accessible to study personnel. Patients will be seen daily by study personnel through the first 7 days for data collection, protocol adherence, and collection of research samples. Beyond study day 7 patient status will be monitored by examining the medical record and, as needed, bedside visit. Study personnel will complete CRFs for ICU discharge, study day 28 status, and hospital discharge. The hospital discharge CRF will contain patient disposition and contact numbers, including the patient's LAR to facilitate 60-day and 90-day follow-up.

3.6/ Safeguards for Vulnerable Population

All potential CHILL-pilot subjects will be considered vulnerable because they will be cognitively impaired as a result of their illness and treatment. Informed consent will be obtained from an LAR and subjects will be re-consented once they regain decision-making capacity as determined using a capacity assessment tool that has been approved by the UMB IRB. Prisoners and pregnant women are excluded. Rules for early termination of hypothermia and NMB have been developed.

3.7/ Outreach to Minorities and Women

The expected COVID-CHILL-pilot patient population is well-represented in minorities and women. Based on our experience with ARDSNet, we expect our study composition to be ~44% African American, 9% Hispanic, and 45% white and ~50% female. The composition of the 64 patients in our CHILL retrospective and open-label pilot study 38 was 60.9% Caucasian, 34.4% African American, 4.6% Hispanic, and 3.1% Asian, and 41% female. There are no exclusions based on race, ethnicity, or gender. Pregnancy will be an exclusion because there are no data to insure safety of mild hypothermia for the fetus. Pregnancy testing will be performed in all women of child-bearing age prior to enrollment.

3.8/ Engagement of Clinical Community to Encourage Recruitment

Presentations about CHILL-pilot will be given as Medical and Pulmonary Grand Rounds at UMMC and to the UMMC critical care committee. Drs. Hasday and Shanholtz and coordinator will educate staff and physicians for all participating ICUs about the CHILL-pilot trial. Signs with information about the CHILL-pilot trial including inclusion and exclusion criteria and easy contact information will be prominently displayed in all participating ICUs.

4/ Screening

Refer to Screening Worksheet and Screening CRF. All patients in participating ICUs (UMMC MICU, T6S, 10W) who are 18-65 years old, have a PCR-documented COVID diagnosis and intubated or have a tracheostomy in place and have been receiving mechanical ventilation for <7 days will be evaluated for enrollment using the Screening Worksheet. If any of the

disqualifying exclusion criteria listed on the Screening/enrollment/randomization CRF are identified, the patient will be excluded. Otherwise they will be evaluated for inclusion criteria and enrolled or followed until they meet inclusion criteria or exit the inclusion window. The 3-digit study ID number and a unique 3-leter patient identifier will be supplied by the on-line Screening Log Tool (on the UMB OneDrive). Demographic information and final enrollment status, and the reason for exclusion (if applicable) will be entered in the on-line screening log and on the Screening CRF along with the 3-digit study ID and 3-letter patient identifier. Those patients who meet enrollment criteria will be offered enrollment. We anticipate that all consent will be obtained from the patients' Legally Authorized Representative (LAR). If consent is obtained, the patient will be enrolled and the "Yes" box about consent (line 11) will be checked. If the patient meets enrollment criteria but consent cannot be obtained, the patient will be excluded from the study.

5/ Subject Enrollment and Randomization Procedures

If the patient meets the P/F ratio criterion for randomization (from ABG or imputed from SpO2), they will be randomized simultaneously with enrollment. Otherwise their P/F ratio will be followed until it is <200 or they exit the 48h ARDS window. If the patient meets the P/F ratio criterion within the ARDS window, mark the "Yes" box about randomization on line 12, otherwise check the "No" box. If the patient is randomized, collect the baseline blood sample, obtain the treatment assignment using the on-line assignment tool, enter the randomization date and time on line 14 and the treatment assignment on line 15. Once Randomized, baseline information will be recorded on the Baseline Data CRF and, if assigned to the Therapeutic Hypothermia arm, sedation, NMB, and cooling will begin as soon as possible.

6/ Study Visit Schedule/Schedule of Events (see Gantt chart below)

DAYS	-2	0	1	2	3	4	7	8-27	28	ICU DC	Hospital DC	60	90
Screening data, consent, enrollment, monitor for randomization	X												
Pregnancy test (F)		F											
Randomization, baseline data, start assigned temperature management		X											
Q2h vital signs (e.g. SpO2, mean airway pressure, core temperature)		X	X	X	X	X	X						
Temperature management protocol		X	X	X	X								
ABGs		A	A	A	A	A	A						
Basic metabolic panel, CBC (times per day)		2	2	2	2	2	1						
Blood sugars (times per day)		4	4	4	4	A	A						
Research blood sample collection		X	X	X	X	X	X						
Ventilator and respiratory parameters	X	X	R	R	R	R	R						
Fluid management		X	X	X	X	X	X						
NMB status	X	X	X	X	X	X	X						
Medication review (pressors, steroids, inhaled vasodilators)		X	X	X	X	X	X						

Monitor for AEs		X	X	X	X	X	X	X	X	x	x	X	X
Calculation 28-day VFDs, ICU-FDs									X				
MOCA										X	X		
Assess Vital and functional status		X	X	X	X	X	X	X	X	x	x	X	X

X = Required (time not specified)
A = When Available
R = Measured during daily reference measurements (0600-1000). When more than one value is available, the value obtained closest to 8 a.m. will be recorded.
F = Required on females of reproductive age.

7/ Study Measurements

Both arms will receive the same standard of care procedures listed below.

7.1/ Vital signs

Heart rate, Blood Pressure, Respiratory rate, Pulse oximetry, Core temperature (esophageal or rectal, temperature sensing bladder catheters, or pulmonary artery catheters, if present). All vital signs will be measured by standard of care and recorded as per study data collection requirements.

7.2/ Ventilatory and respiratory parameters

Ventilatory and respiratory parameters (Peak Airway Pressure (Ppeak), Airway Plateau Pressure (Pplat), Positive End Expiratory Pressure (PEEP) and Mean Airway Pressure ($P\overline{aw}$) will be obtained from standard of care mechanical ventilation record. Driving Pressure is calculated calculated as the difference between airway plateau pressure and end-expiratory pressure (Pplat – PEEP) during a breath without spontaneous ventilator effort and Oxygen saturation index (OSI). This will be calculated as the product of mean airway pressure, fraction of inspired oxygen, and 100, divided by pulse oxygen saturation ($P\overline{aw} \times FIO_2 \times 100/SpO_2$) will be calculated and recorded per study data collection requirements.

7.3/ 5.3 Blood Laboratory values data collection

Hematology (WBC, Hgb, Hct, Platelets), Chemistry (Potassium, Bicarbonate, BUN, Creatinine, Glucose, Magnesium, Phosphate, Albumin, Bilirubin AST/ALT results measured by standard of care and recorded as per study data collection requirements.

7.4/ Blood sugar

Blood sugar will be measured by fingerstick and analyzed with a handheld point-of-care glucometer (Accu-chek, Roche) and reported in the EMR by the nurse at the bedside who is not part of the study team.

7.5/ Fluid management

Fluid management of ARDS patients enrolled in the CHILL Study, excluding patient in shock, will follow clinical guidelines of conservative approach fluid management.
This conservative fluid management approach will represent a simplification of the algorithm utilized in the ARDS Network FACTT study [7]. If not already being utilized, this conservative fluid management approach must be initiated within four hours of randomization and continued until the subject has reached unassisted breathing (UAB) or study day 7, whichever occurs first.

1. Discontinue maintenance fluids.
2. Continue medications and nutrition.
3. Manage electrolytes and blood products per usual practice.

4. For shock, use any combination of fluid boluses and vasopressor(s) to achieve mean arterial pressure ≥ 60mm Hg as fast as possible.
   - Consider assessing for hypovolemia with bedside ultrasound (IVC collapsibility) and/or fluid responsiveness with passive leg raise (PLR) before bolusing fluid
   - Recommended fluid bolus = 15mL/kg crystalloid rounded to nearest 250 mL or 1 unit packed red cells or 25g albumin
   - Wean vasopressors as quickly as tolerated beginning 4hr after blood pressure has stabilized.
5. Withhold diuretic therapy in **renal failure** and until 12h after last fluid bolus or vasopressor use.
   - Renal failure defined as dialysis dependence, oliguria with serum creatinine > 3mg/dL, or oliguria with serum creatinine 0–3 with urinary indices indicative of acute kidney injury).

Table 1: Guidelines for Fluid Management

<table>
<tr><th rowspan="2">CVP[a]</th><th rowspan="2">PAOP (optional)</th><th colspan="2">MAP ≥ 60 mm Hg AND off vasopressors for ≥ 12h</th></tr>
<tr><th>Average urine output < 0.5 ml/kg/hr</th><th>Average urine output ≥ 0.5 ml/kg/hr</th></tr>
<tr><td>>8[b]</td><td>> 12[b]</td><td>Furosemide[e]
Reassess in 1h</td><td rowspan="2">Furosemide[e]
Reassess in 4h</td></tr>
<tr><td>4-8[c]</td><td>8-12[c]</td><td rowspan="2">Give fluid bolus
Reassess in 1h</td></tr>
<tr><td>< 4[d]</td><td>< 8[d]</td><td>No intervention
Reassess in 4h</td></tr>
</table>

[a]If no central venous catheter (CVC), peripherally inserted central catheter (PICC), or pulmonary artery catheter (PAC, Swan-Ganz catheter), consider assessing volume status with ultrasound of IVC or NT-proBNP. If these assessments are normal, or not available, treat as euvolemic (CVP 4-8 or PAOP 8-12).

[b]If no CVC, PICC, or PAC present, can substitute distended IVC on bedside ultrasound or elevated NT-proBNP (adjusted for age)

[c]If no CVC, PICC, or PAC present, can substitute normal caliber IVC (neither distended nor collapsible) on bedside ultrasound or normal NT-proBNP (adjusted for age). If these assessments are unavailable consider this euvolemic.

[e]If no CVC, PICC, or PAC present, can substitute collapsible IVC on bedside ultrasound

[e]Recommended Furosemide dosing = begin with 20 mg bolus or 3 mg / hr infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or maximum infusion rate of 24 mg / hr or 160 mg bolus reached. Do not exceed 620 mg/day. Also, if patient has heart failure, consider treatment with dobutamine.

Fluid intake and output (I/O) will be obtained from EMR and recorded per study data collection requirements. I/Os will be computed every 24 hours for 0800-0759.

7.6/ Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment tool (www.mocatest.org) 8.1 will be administered by a study investigator at ICU and hospital discharge. Due to infection control concerns regarding the cleaning of tablet computers the test will be administered on paper. All study investigators will register and receive online training and certification in MoCA at the website listed above.

8/ Study Interventions

Temperature management:

1. Therapeutic Hypothermia Arm: The participating ICUs share an established institutional protocol for NMB and TH, which will facilitate rapid mobilization of treatment following randomization. Sedation will be adjusted to achieve a RASS -4 score and cisatracurium (Nimbex™) will be initiated and adjusted to the lowest rate that achieves nerve stimulation response of 2 twitches in train-of-four monitoring, reduction in ventilator dyssynchrony to acceptable levels, and elimination of shivering. NMB will be continued through the rewarming phase at least until core temperature reaches 35.5°C (~54h total time). Note that if the supply of Nimbex in the Clinical Pharmacy is insufficient to treat the subject, a supply of study-only Nimbex is available in the Investigational Drug Service Pharmacy.

Since the objective of CHILL-pilot is to test the effectiveness of cooling to a target temperature rather than the performance of a specific cooling device, patients in the TH arm will be cooled using one of the institution's two FDA-approved surface cooling devices, Blanketrol II cooling blankets or Arctic Sun™ cooling system. Core temperature will be reduced to 34°-35°C as quickly as possible and TH maintained for 48h. Patients will then be rewarmed to 36°C by 0.3°C/h and the cooling device removed. Post-cooling fever suppression is not part of the CHILL-pilot protocol. Cooling parameters were selected to optimize risk:benefit ratio. The criteria for early termination of hypothermia are persistent severe bradycardia (heart rate < 30 associated with mean arterial pressure <65 without vasopressor agents), uncontrolled bleeding, and intractable ventricular arrhythmias.

Placing the order to initiate hypothermia:

- Order sedation to RASS >-4 and Nimbex to achieve 2 twitches on train-of-four testing.
- Enter UMMC MED-CC Hypothermia Following Arrest Supplemental order set in Epic with the following modifications:
  i. De-select: Capnography, CVP monitoring, SvO2 monitoring, NPO, Bair Hugger, Maintain MAPBP > 80 mmHg, Document Water temperature, CXR, sodium chloride 0.9% bolus, fentanyl, and vecuronium, cistracurium.
  ii. Under Chemistry, select Comprehensive Metabolic Panel
  iii. Modify Hyper/Hypothermia order by changing stop date from 24h to 48 h and changing comments to: "Lower patient's temperature to **34 – 35C** as quickly as possible per protocol. Maintain **core temperature between 34 and 35C for 48 hours**. AT **48 hrs** after the initial cooling, re-warm patient no faster than **0.3** degree C per hour to **36C**." Delete "Then maintain ≤ 37C for 48 hours." (Changes from Epic order set are underlined and bolded.) These instructions have been added to the Randomization CRF.

2. Usual Temperature Management Arm: Controls will receive sedation and NMB as clinically indicated to achieve synchrony with the ventilator. During the 54h post-randomization period (corresponding with cooling and rewarming in the TH arm), acetaminophen will be given for core temperature >38°C and surface cooling initiated for core temperature >38.5°C and adjusted to maintain temperature ≤38°C. If patients are hypothermic (core temperature <35.5°C), surface warming will be initiated to restore core temperature to 37°C. Following the 54h treatment period, temperature management in both arms will be directed by the ICU team.

9/ Case Report Forms

Appended.

10/Question by Question (QxQ) Instructions

10.1/ Screening, enrollment, randomization CRF

- Only screen if patient is 18-65 years old and has been intubated or trached and requiring mechanical ventilation for <7 days.
- Record site ID code (01 for UMB), 3-digit study ID and a unique 3-letter patient identifier in the indicated fields at the top of each page (assigned using the on-line CHILL Screening Log tool).
- Record your name on line 1 (Name of Screener).
- Record date and time (2400 clock) screening was initiated in indicated fields on line 2.
- Indicate type of unit on line 3.
- Enter gender on line 4
- Enter birth date on line 5
- Enter whether Hispanic or Latino on line 6
- Enter race on line 7.
- If the answers on lines 3 and 4 are both “Yes,” indicate all applicable exclusion criteria under line 8 by checking the appropriate boxes.
- If any of the listed exclusion criteria on line 8 are present, the patient is not eligible for the study; Check the “No” box on line 11, complete the on-line screening log and stop.
- If none of the exclusion criteria on line 8 are present, proceed with the Berlin criteria checklist. Indicate the time and date of each screen for ARDS criteria (line 10), and check the appropriate “Yes/No” box for each criterion: (a) whether a CXR or CT was performed; (b) whether bilateral pulmonary infiltrates are present and (c) whether based on available clinical, physiological, and echocardiographic data you can exclude cardiogenic cause as the sole etiology. If the answer to all 3 questions is “Yes” and the patient is within the 7 day mechanical ventilation window, check “Yes” on line 11. Otherwise Click the “No” box and STOP.
- If Berlin ARDS mechanical ventilation and bilateral infiltrates criteria have been met and no exclusion criteria are present, attempt to obtain informed consent. If consent is not provided, check the “No” box and STOP, otherwise check the “Yes” box and proceed to the P/F ratio table on line 13.

- Monitor for qualifying P/F ratio using the P/F ratio table. For each ventilator day, check the appropriate "Yes/No" box for PEEP≥8 cm H_2O, whether P/F<200, whether the value was calculated from the measured PaO_2 ("M") or imputed ("I") from the SpO_2. Record the value for the P/F ratio and the date and time it was measured. If patient meets all Berlin criteria, including P/F ratio < 200 within 7 days of onset of intubation/mechanical ventilation, check the "Yes" box on line 14, collect the baseline blood sample, and proceed with randomization; otherwise, check the "No" box and STOP.
- If randomizing, record whether the patient is receiving intermittent prone positioning at the time of randomization on line 15.
- Obtain the treatment assignment using the on-line assignment tool, record the randomization date and time on line 16 and record the treatment assignment on line 17.
- For patients randomized to the cooling arm, initiate sedation, NMB, and cooling.

10.2/ Enrollment note

- Fill in patient's name and Medical record number on the Clinical Research Enrollment note template, sign, and date, and place in the bedside chart, then submit to be scanned for the Electronic Medical Record.

10.3/ Baseline Data CRF

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Record your name and the date and time CRF was completed in the indicated fields on line 1.
- Record hospital admission date in indicated field on line 2.
- Indicate the type of ICU patient is admitted to by checking the appropriate box on line 3.
- Record date and time of current ICU admission in indicated fields on line 4.
- Check appropriate box to indicate clinical location from which patient was admitted to the participating ICU on line 5.
- Check appropriate box to indicate patient's level of independence prior to the current hospitalization on line 6.
- Check appropriate box on line 7 to indicate cigarette smoking status and record the number of pack-years and quit date where appropriate.
- Indicate whether the patient had surgery within the last week prior to randomization on line 8 by checking the appropriate "Yes/No" box and, if "Yes," record the date in the appropriate field and check the box(es) for the type of surgery (Check all that apply). If "No" skip to question line 9.
- On line 9, check the appropriate "Yes or No" box for each listed chronic health problem and additional past medical history.
- On line 10, enter the highest and lowest core temperature recorded in the electronic medical record for the 24 hours preceding randomization in the indicated fields and check the box for the body location of the temperature measurement. Do not record peripheral temperatures unless a core temperature measurement is not available. If only a single

value, record in the "Lowest" field and check the single box. If no temperature data, check the "None" box.

- On line 11, enter the highest and lowest values for the systolic BP, mean arterial pressure, heart rate, and respiratory rate recorded in the medical record for the 24 hours preceding randomization in the indicated fields. If only a single value record in the "Lowest" field and check "Single" box.
- Indicate whether the lowest respiratory rate recorded was while the patient was mechanically ventilated by checking the appropriate "Yes/No" box on line 12.
- Record the urine output, the total output (urine, stool, tube drainage, and negative CRRT balance), and the total intake for the 24 hours preceding randomization in the appropriate fields beginning on line 13.
- Beginning on line 14, enter the highest and lowest values for each indicated laboratory value in the 24 hours preceding randomization. If there is only one value, record it in the "Lowest" field, and click the "Single" box. If no data available for this period check the "None" box.
- On line 15, enter the lowest recorded **post-intubation** SpO_2 value in the past 24 hours preceding randomization, the date/time recorded, the corresponding FiO2, and the most concurrently measured Mean Airway Pressure and PEEP. For the same period, record the arterial blood gas with the lowest PaO_2, including the pH, $PaCO_2$, the PaO_2, and the corresponding FiO_2 in the indicated fields. If an ABG was not done during this period, check the "None" box.
- On line 16 enter the date and time of the most recently recorded ventilator settings prior to randomization.
- Indicate the ventilator mode used at that time by checking the appropriate box under line 17.
- If mode is volume targeted, enter the set tidal volume in milliliters in the appropriate field on line 18.
- If mode is pressure targeted, enter the set inspiratory time in seconds and the inspiratory pressure in cm H_2O in the appropriate fields on line 19.
- Enter the respiratory rate in breaths per minute and PEEP in cm H_2O in the appropriate fields on line 20. If breathing mode is spontaneous without a back-up rate, write "NA" in the respiratory rate field.
- If the patient is ventilated using APRV/BiVENT, enter the $P_{1/high}$, $P_{2/PEEP}$ in cm H2O and the $T_{1/high}$ and $T_{2/PEEP}$ in seconds in the appropriate fields on line 21.
- Enter the respiratory parameters measured most recently recorded in the Electronic Medical Record prior to randomization in the indicated fields beginning on line 22, including the tidal volume in ml, respiratory rate in breaths per minute, minute ventilation in L/min, SpO2 as %, Plateau pressure in cm H_2O and the corresponding F_iO_2 and PEEP, the peak inspiratory pressure and mean airway pressure in cm H_2O and the I:E ratio.
- Complete the ARDSNet checklist by checking the appropriate "Yes/No" box about each listed ventilatory parameter at the time of randomization. If any answers are "No," request respiratory therapy to adjust the ventilatory setting to comply with ARDSNet guidelines, record the date and time the changes are made, and on line 23, record the post-change measured parameters on line 24.

- Record height, weight, predicted ideal weight (for purposes of adjusting tidal volume), and the most recently recorded heart rate (beats per minute), systolic, diastolic, and mean arterial pressures in mm Hg, CVP in cm H_2O, and body temperature in °C prior to randomization in the indicated fields beginning on line 25. Convert °F to °C using the following formula:

  °C = (°F – 32) X 5/9

  If CVP is not available, check the "CVP not available" box.
- Indicate if the patient received vasopressor support at any time during the 24 hours prior to randomization by checking the appropriate "Yes/No" box on line 26. If "Yes," check the box next to each of the agents received, the highest infusion rate received, check box for appropriate units, and the total time receiving any vasopressor support.
- Indicate whether the patient is receiving an inhaled vasodilator at the time of randomization by checking the appropriate "Yes/No" box on line 27. If "Yes," enter date and time the current administration was started in the indicated field on line 28 and identify the agent used by checking the appropriate box and the.
- Indicate whether the patient received corticosteroids in the 24 hours prior to randomization by checking the appropriate "Yes/No" box on line 29 and, if "Yes," enter the total dose in hydrocortisone equivalents using the conversion, 1 mg prednisone or methylprednisolone = 4 mg hydrocortisone and 1 mg dexamethasone = 25 mg hydrocortisone.
- List any COVID-19 drugs given (including investigational).
- Indicate the Date and Time NMB was started in the appropriate fields on line 31.
- If a proning protocol has been initiated, indicate the time and date the protocol was initiated in the appropriate filed on line 32. If a proning protocol has not been initiated, write "NA" in the month field.
- If the patient is in the hypothermia group, record the date and time that cooling was initiated in the appropriate fields on line 33, indicate the cooling method used by checking the appropriate box on line 34. If the patient is in the Usual Temperature Management group, write "NA" in the month field on line 33.
- Indicate whether the baseline research blood sample was collected by checking the appropriate Yes/No" box on line 35.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 36.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 37.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 38.
- Indicate the location of the sample in the freezer and the displayed freezer temperature at the time the samples were placed in the indicated fields on line 39.
- Enter contact information for patient, LAR, and any additional potential contacts for 60- and 90-day follow-up.

10.4/ Day 1 Data CRF

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.

- Record your name and the date and time CRF was completed in the indicated fields on line 1.
- Indicate vital status by checking appropriate Alive/Dead box on line 2 and, if "Dead," record date and time of death in the indicated fields on line 3 and check the box next to the most appropriate cause of death (based on information from the discharge summary and discussion with the ICU provider team) on line 4.
- Indicate whether patient is still receiving NMB by checking appropriate "Yes/No" box on line 5. If "Yes," skip to line 9, otherwise record date and time it was discontinued on line 6, check the appropriate box for the major reason it was discontinued on line 7 (only check one box), and record the time neuromuscular function return (based on return of 4 twitches on train of 4 testing) in the indicated fields on line 8 or check the "Did not return" box if neuromuscular function did not return by 0800 of study day 1.
- Indicate whether the patient is in the hypothermia by checking the appropriate "Yes/No" box on line 9. If "No" skip to question 14. If "yes" indicate the time in minutes between randomization and first reaching target core temperature (34°-35°C) and the time in minutes between initiation of cooling and first reaching target core temperature in the indicated fields on line 10. Indicate whether the patient is still being cooled as of 0800 of study day 1 by checking the appropriate "Yes/No" box on line 11. If "Yes" skip to question 15. If "No," record date and time cooling was stopped on line 12 and the most closely applicable reason for discontinuing cooling by checking the appropriate box on line 13 (check only one box).
- For patients in the control arm, indicate whether they received therapeutic hypothermia (intentional cooling to core temperature <36°C) since randomization by checking the appropriate "Yes/No" box on line 14. If in the hypothermia arm, check the "N/A" box.
- Indicate whether patient is still intubated (or if the patient has a tracheostomy, whether they are still receiving continuous mechanical ventilation (with <24h interruption) by checking appropriate "Yes/No" box on line 15 and if "No" record date and time patient was extubated or was UAB for ≥48h in the indicated fields.
- Indicate whether patient was started on renal replacement therapy (RRT) since randomization by checking appropriate "Yes/No" box on line 16. If the patient was already receiving RRT, check the N/A box.
- If the patient was already receiving RRT, indicate whether it was discontinued since randomization by checking appropriate "Yes/No" box on line 17. If the patient was not previously receiving RRT, check the N/A box.
- On line 18, please if indicate if any of the adverse events occurred since randomization by checking the appropriate "Yes/No" boxes.
- Enter the lowest and highest values since randomization from the EMR for systolic and diastolic blood pressure and mean arterial pressure in mm Hg in the appropriate fields on line 19. Record the lowest and highest values for CVP in cm H2O. If no CVP measurements check the "CVP not available" box. If only one measurement for any of the vital signs, enter the value in the "Lowest" CVP box and check the "Single" box.
- On line 20, record date and time of randomization and initiation of cooling or check "Not cooled" box if patient was not cooled.

- In the table on line 21, check the box for the time period when patient was randomized. Then for each 2-hour period beginning with randomization and continuing until 0800 on the day after randomization the highest and lowest recorded core temperatures, check the box indicating the location of the temperature probe, and enter the lowest recorded SpO_2 value, the corresponding F_iO_2, and the most concurrently measured Mean Airway Pressure. If there is only a single temperature measurement during the period, record in the "Lowest" field and check the "Single value" box. If there are no SpO_2 measurements during a 2-hour period, indicate by checking the "None" Box for SpO_2. If the patient was receiving supplemental oxygen by NC, calculate the FiO_2 using the formula: $FiO_2 = 0.21 + 0.03$ x flow rate in LPM.
- Indicate whether the patient received corticosteroids since randomization by checking the appropriate "Yes/No" box on line 22. If "Yes," enter the total dose in hydrocortisone equivalents using the conversion, 1 mg prednisone or methylprednisolone = 4 mg hydrocortisone and 1 mg dexamethasone = 25 mg hydrocortisone.
- Indicate whether the patient received an inhaled vasodilator since randomization by checking the appropriate "Yes/No" box on line 23. If "Yes," indicate which agent(s) by checking the appropriate box(es) and the total hours one or more of the agents were administered in the indicated field.
- Indicate if the patient received vasopressor support at any time since randomization by checking the appropriate "Yes/No" box on line 24. If "Yes," check the box next to each of the agents that was received, the highest infusion rate (and units) received, and the total hours receiving any vasopressor support. If "no" skip to question 25.
- Beginning on line 25, record the highest and lowest values for each indicated laboratory value since randomization. If there is only one value, record it in the lowest value field, and click the single value box. If there are no data, check the "None" box.
- In the appropriate fields in table beginning on line 26, enter the lowest and highest blood glucose values (from finger sticks) and the date and time of the measurements for each 6-hour period since randomization. If there is only a single value, record in the "Lowest Glucose" field and and check the "Single Value" box for that 6-hour time period. If there are no glucose measurements, click the "None" box for that 6-hour time period.
- Indicate all ventilator modes used since randomization by checking the appropriate boxes under line 27 and circle the mode used at 0800.
- Indicate whether the patient was extubated since randomization by checking the appropriate "Yes/No" box on line 28 and, if extubated, enter the time and date in the appropriate fields.
- Record the highest and lowest measured tidal volumes in ml during mechanical ventilation since randomization in the appropriate fields on line 29.
- Based on the EMR, estimate the total time since randomization in hours in which tidal volume exceeded 7 ml/kg during mechanical ventilation and record in field on line 30.
- Enter the highest and lowest PEEP and Mean airway pressure in cm H_2O during mechanical ventilation since randomization in the appropriate fields on lines 31 and 32, respectively.
- If still intubated between 0600 and 1000 on the day after randomization, record the plateau pressure and associated PEEP measured in this time interval in the indicated fields beginning on line 33. If multiple values are present, enter the value closest to 0800. If no

values from that time period check the "No Values" box. If the patient was not intubated during this time period check the "Not intubated" box.

- If arterial blood gasses are performed, enter the highest and lowest PaO_2 and associated FiO2 since randomization in the appropriate fields on line 34. If only a single value enter the PaO2 and FiO2 values in the "Lowest" field and check the "Single value" box. If no arterial blood gasses were performed, check the "None" box.
- Record total intake in ml in the field on line 35.
- Record the total output (including net volume removed by RRT) between randomization and 0800 in the field on line 36.
- Indicate whether the day 1 research blood sample was collected by checking the appropriate "Yes/No" box on line 37.
- Record the date and time the research blood sample was collected and the time it wasprocessed in the appropriate fields on line 38.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 39.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 40.
- Indicate the location of the sample in the freezer and the displayed freezer temperature at the time the samples were placed in the indicated fields on line 41.

10.5/ Day 2 and 3 Data CRFs

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Record your name and the date and time CRF was completed in the indicated fields on line 1.
- Indicate vital status by checking appropriate Alive/Dead box on line 2 and, if "Dead," record date and time of death in the indicated fields on line 3 and check the box next to the most appropriate cause of death (based on information from the discharge summary and discussion with the ICU provider team) on line 4.
- Indicate whether patient is still receiving NMB by checking appropriate "Yes/No" box on line 5 and, if "No," record date and time it was discontinued on line 6, check the appropriate box for the major reason it was discontinued on line 7 (only check one box), and record the time neuromuscular function return (based on return of 4 twitches on train of 4 testing) in the indicated fields on line 8 or check the "no" box if neuromuscular function had not yet returned.
- Indicate whether the patient is in the hypothermia by checking the appropriate "Yes/No" box on line 9. If "No" skip to question 13. If "yes" indicate whether the patient is still being cooled as of 0800 of study day 2 (or 3) by checking the appropriate "Yes/No" box on line 10. If "Yes" skip to question 14. If "No," record date and time cooling was stopped on line 11 and indicate the most closely applicable reason for discontinuing cooling by checking the appropriate box (check only one box) on line 12 and skip to line 14..
- For patients in the Control arm, indicate whether they received therapeutic hypothermia (intentional cooling to core temperature <36°C) since randomization by checking the appropriate Yes/No box on line 13. If in the hypothermia arm, check the "N/A" box.

- Indicate whether patient is still intubated (or if the patient has a tracheostomy, whether they are still receiving continuous mechanical ventilation (with <24h interruption) by checking appropriate yes/no box on line 14 and if "No" record date and time patient was extubated or was UAB for ≥48h in the indicated fields.
- Indicate whether patient was started on renal replacement therapy (RRT) in the past 24 hours by checking appropriate "Yes/No" box on line 15. If the patient was already receiving RRT, check the N/A box.
- If the patient was already receiving RRT, indicate whether it was discontinued in the past 24 hours by checking appropriate "Yes/No" box on line 16. If the patient was not previously receiving RRT, check the N/A box.
- On line 17, please if indicate if any of the adverse events occurred in the last 24 hours by checking the appropriate "Yes/No" boxes.
- Enter the lowest and highest values since randomization from the EMR for systolic and diastolic blood pressure and mean arterial pressure in mm Hg in the appropriate fields on line 15. Record the lowest and highest values for CVP in cm H_2O. If no CVP measurements check the "CVP not available" box. If only one measurement for any of the vital signs, enter the value in the "Lowest" CVP box and check the "Single" box.
- In the table on line 19 enter for each 2-hour period in the previous 24 hours the highest and lowest recorded core temperatures, check the box next to the location of the probe, and enter the lowest recorded SpO_2 value, the corresponding F_iO_2, and the most concurrently measured Mean Airway Pressure. If there is only a single temperature measurement during the period, record in the "Lowest" field and check the "Single value" box. If there are no SpO_2 measurements during a 2-hour period, indicate by checking the "None" Box for SpO2. If the patient was receiving supplemental oxygen by NC, calculate the FiO2 using the formula: FiO2 = 0.21 + 0.03 x flow rate in LPM.
- Indicate whether the patient received corticosteroids in the last 24 hours by checking the appropriate "Yes/No" box on line 20. If "Yes," enter the total dose in hydrocortisone equivalents using the conversion, 1 mg prednisone or methylprednisolone = 4 mg hydrocortisone and 1 mg dexamethasone = 25 mg hydrocortisone.
- Indicate whether the patient received an inhaled vasodilator in the last 24 hours by checking the appropriate "Yes/No" box on line 21. If "Yes," indicate which agent by checking the appropriate box and recording the total number of hours the at least one agent was administered.
- Indicate if the patient received vasopressor support at any time since randomization by checking the appropriate "Yes/No" box on line 22. If "Yes," check the box next to each of the agents that was received, the highest infusion rate (and units) received, and the total hours receiving any vasopressor support. If "No" skip to question 23.
- . On line 23, indicate whether a proning protocol was started or stopped in the preceding 24 hours.
- Beginning on line 24, record the lowest and highest values for each indicated laboratory value since randomization. If there is only one value, record it in the lowest value field, and click the "Single" box. If there are no data, check the "None" box.
- In the appropriate fields in table beginning on line 25, enter the lowest and highest blood glucose values (from finger sticks) and the date and time of the measurements for each 6-

hour period since randomization. If there is only a single value, record in the "Lowest Glucose" field and check the "Single Value" box for that 6-hour time period. If there are no glucose measurements, click the "None" box for that 6-hour time period.

- If the patient was extubated prior to Study Day 2 (or 3) skip to question 34.
- If intubated and receiving mechanical ventilation for any part of day 2 (or 3) indicate all ventilator modes used in the last 24 hours by checking the appropriate boxes under line 26 and circle the mode used at 0800.
- Indicate whether the patient was extubated in the last 24 hours by checking the appropriate "Yes/No" box on line 27 and, if extubated, enter the time and date in the appropriate fields.
- Record the highest and lowest measured tidal volumes in ml in the last 24 hours in the appropriate fields on line 28.
- Based on the EMR, estimate the total time in hours in the last 24 hours in which tidal volume exceeded 7 ml/kg and record in field on line 29.
- Enter the highest and lowest PEEP and Mean airway pressure in cm H_2O in the last 24 hours in the appropriate fields on lines 30 and 31, respectively.
- If still intubated between 0600 and 1000 on study day 2 (or 3), record the plateau pressure and associated PEEP measured in this time interval in the indicated fields beginning on line 32. If multiple values are present, enter the value closest to 0800. If no values from that time period check the "No Values" box. If the patient was not intubated during this time period check the "Not intubated" box.
- If arterial blood gasses are performed, enter the highest and lowest PaO_2 and associated F_iO_2 since randomization in the appropriate fields on line 29. If only a single value enter the PaO_2 and F_iO_2 values in the "Lowest" field and check the "Single value" box. If no arterial blood gasses were performed, check the "None" box.
- Enter total intake in ml in the field on line 34.
- Enter total output (including net volume removed by RRT) in the last 24 hours in the field on line 35.
- Indicate whether the research blood sample was collected by checking the appropriate "Yes/No" box on line 36.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 37.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 38.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 39.
- Indicate the location of the sample in the freezer and the displayed freezer temperature at the time the samples were placed in the indicated fields on line 40.

10.6/ Day 4 Data CRF

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Record your name and the date and time CRF was completed in the indicated fields on line 1.

- Indicate vital status by checking appropriate Alive/Dead box on line 2 and, if "Dead," record date and time of death in the indicated fields on line 3 and check the box next to the most appropriate cause of death (based on information from the discharge summary and discussion with the ICU provider team) on line 4.
- Indicate whether patient is still receiving NMB by checking appropriate "Yes/No" box on line 5 and, if "No," record date and time it was discontinued on line 6, check the appropriate box for the major reason it was discontinued on line 7 (only check one box), and record the time neuromuscular function return (based on return of 4 twitches on train of 4 testing) in the indicated fields on line 8 or check the "no" box if neuromuscular function did not return within the prior 24 hours.
- Indicate whether the patient is in the hypothermia by checking the appropriate "Yes/No" box on line 9. If "No" skip to question 13. If "yes" indicate whether the patient completed 48 hours of hypothermia by checking the appropriate "Yes/No" box on line 10. If "Yes" skip to question 14. If "No," record date and time cooling was stopped in the indicated fields and indicate the most closely applicable reason for early discontinuation of cooling by checking the appropriate box (check only one box).
- For patients in the usual temperature management arm, indicate whether they received therapeutic hypothermia (intentional cooling to core temperature <36°C) since randomization by checking the appropriate Yes/No box on line 13. If in the hypothermia arm, check the "N/A" box.
- Indicate whether patient is still intubated (or if the patient has a tracheostomy, whether they are still receiving continuous mechanical ventilation (with <24h interruption) by checking appropriate yes/no box on line 14 and if "No" record date and time patient was extubated or was UAB for ≥48h in the indicated fields.
- Indicate whether patient was started on renal replacement therapy (RRT) in the past 24 hours by checking appropriate "Yes/No" box on line 15. If the patient was already receiving RRT, check the N/A box.
- If the patient was already receiving RRT, indicate whether it was discontinued in the past 24 hours by checking appropriate "Yes/No" box on line 16. If the patient was not previously receiving RRT, check the N/A box.
- On line 17, please if indicate if any of the adverse events occurred in the last 24 hours by checking the appropriate "Yes/No" boxes.
- Enter the lowest and highest values since randomization from the EMR for systolic and diastolic blood pressure and mean arterial pressure in mm Hg in the appropriate fields on line 18. Record the lowest and highest values for CVP in cm H2O. If no CVP measurements check the "CVP not available" box. If only one measurement for any of the vital signs, enter the value in the "Lowest" CVP box and check the "Single" box.
- In the table on line 19 enter for each 2-hour period in the previous 24 hours the highest and lowest recorded core temperatures, check the box next to the location of the probe, and enter the lowest recorded SpO_2 value, the corresponding F_iO_2, and the most concurrently measured Mean Airway Pressure. If there is only a single temperature measurement during the period, record in the "Lowest" field and check the "Single value" box. If there are no SpO_2 measurements during a 2-hour period, indicate by checking the "None" Box for SpO_2. If

the patient was receiving supplemental oxygen by NC, calculate the F_iO_2 using the formula: F_iO_2 = 0.21 + 0.03 x flow rate in LPM.

- Indicate whether the patient received corticosteroids in the last 24 hours by checking the appropriate "Yes/No" box on line 20. If "Yes," enter the total dose in hydrocortisone equivalents using the conversion, 1 mg prednisone or methylprednisolone = 4 mg hydrocortisone and 1 mg dexamethasone = 25 mg hydrocortisone.
- Indicate whether the patient received an inhaled vasodilator in the last 24 hours by checking the appropriate "Yes/No" box on line 21. If "Yes," indicate which agent by checking the appropriate box and the date and time the current administration was started in the indicated field.
- Indicate if the patient received vasopressor support at any time since randomization by checking the appropriate "Yes/No" box on line 22. If "Yes," check the box next to each of the agents that was received, the highest infusion rate (and units) received, and the total hours receiving any vasopressor support. If "No" skip to question 20.
- Indicate whether proning protocol was initiated or stopped in the previous 24 hours on line 23.
- Beginning on line 24, record the lowest and highest values for each indicated laboratory value since randomization. If there is only one value, record it in the lowest value field, and click the "Single" box. If there are no data, check the "None" box.
- In the appropriate fields in table beginning on line 25, enter the lowest and highest blood glucose values (from finger sticks) and the date and time of the measurements for each 6-hour period since randomization. If there is only a single value, record in the "Lowest Glucose" field and check the "Single Value" box for that 6-hour time period. If there are no glucose measurements, click the "None" box for that 6-hour time period.
- If the patient was extubated prior to Study 4 skip to question 34.
- If intubated and receiving mechanical ventilation for any part of day 4 indicate all ventilator modes used in the last 24 hours by checking the appropriate boxes under line 26 and circle the mode used at 0800.
- Indicate whether the patient was extubated in the last 24 hours by checking the appropriate "Yes/No" box on line 27 and, if extubated, enter the time and date in the appropriate fields.
- Record the highest and lowest measured tidal volumes in ml in the last 24 hours in the appropriate fields on line 28.
- Based on the EMR, estimate the total time in hours in the last 24 hours in which tidal volume exceeded 7 ml/kg and record in field on line 29.
- Enter the highest and lowest PEEP and Mean airway pressure in cm H_2O in the last 24 hours in the appropriate fields on lines 30 and 31, respectively.
- If still intubated between 0600 and 1000 on study day 4, record the plateau pressure and associated PEEP measured in this time interval in the indicated fields beginning on line 32. If multiple values are present, enter the value closest to 0800. If no values from that time period check the "No Values" box. If the patient was not intubated during this time period check the "Not intubated" box.
- If arterial blood gasses are performed, enter the highest and lowest PaO_2 and associated F_iO_2 since randomization in the appropriate fields on line 33. If only a single value enter the

PaO_2 and F_iO_2 values in the "Lowest" field and check the "Single value" box. If no arterial blood gasses were performed, check the "None" box.

- Enter total intake in ml in the field on line 34.
- Enter total output (including net volume removed by RRT) in the last 24 hours in the field on line 35.
- Indicate whether the research blood sample was collected by checking the appropriate "Yes/No" box on line 36.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 37.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 38.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 39.
- Indicate the location of the sample in the freezer and the displayed freezer temperature at the time the samples were placed in the indicated fields on line 40.

10.7/ Day 7 Data CRF

- . Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Record your name and the date and time CRF was completed in the indicated fields on line 1.
- Indicate if still alive by checking appropriate "Yes/No" box on line 2 and, if "No," record date and time of death in the indicated fields on line 3 and check the box next to the most appropriate cause of death (based on information from the discharge summary and discussion with the ICU provider team) on line 4.
- Indicate whether patient is still receiving NMB by checking appropriate "Yes/No" box on line 5 and, if "No," record date and time it was discontinued on line 6, check the appropriate box for the major reason it was discontinued on line 7 (only check one box), and record the time neuromuscular function return (based on return of 4 twitches on train of 4 testing) in the indicated fields on line 8 or check the "no" box if neuromuscular function did not return through day 7.
- Indicate whether patient (regardless of treatment arm) received therapeutic hypothermia (intentional cooling to core temperature <36°C) in the last 72 hours (study days 5-7) by checking the appropriate Yes/No box on line 9 and enter the total time cooled and the loses core temperature in the indicated fields.
- Indicate whether patient is still intubated (or if the patient has a tracheostomy, whether they are still receiving continuous mechanical ventilation (with <24h interruption) by checking appropriate yes/no box on line 10 and if "No" record date and time patient was extubated or was UAB for ≥48h in the indicated fields.
- Indicate whether patient was started on renal replacement therapy (RRT) in the past 24 hours by checking appropriate "Yes/No" box on line 11. If the patient was already receiving RRT, check the N/A box.

- If the patient was already receiving RRT, indicate whether it was discontinued in the past 24 hours by checking appropriate "Yes/No" box on line 12. If the patient was not previously receiving RRT, check the N/A box.
- On line 13, please if indicate if any of the adverse events occurred in the last 24 hours by checking the appropriate "Yes/No" boxes.
- Enter the lowest and highest values since randomization from the EMR for systolic and diastolic blood pressure and mean arterial pressure in mm Hg in the appropriate fields on line 14. Record the lowest and highest values for CVP in cm H2O. If no CVP measurements check the "CVP not available" box. If only one measurement for any of the vital signs, enter the value in the "Lowest" CVP box and check the "Single" box.
- In the table on line 15 enter for each 6-hour period in the previous 24 hours the highest and lowest recorded core temperatures, check the box next to the location of the probe, and enter the lowest recorded SpO_2 value, the corresponding F_iO_2, and the most concurrently measured Mean Airway Pressure. If there is only a single temperature measurement during the period, record in the "Lowest" field and check the "Single value" box. If there are no SpO_2measurements during a 2-hour period, indicate by checking the "None" Box for SpO_2. If the patient was receiving supplemental oxygen by NC, calculate the F_iO_2 using the formula: $F_iO_2 = 0.21 + 0.03$ x flow rate in LPM.
- Indicate whether the patient received corticosteroids in the last 24 hours by checking the appropriate "Yes/No" box on line 16 If "Yes," enter the total dose in hydrocortisone equivalents using the conversion, 1 mg prednisone or methylprednisolone = 4 mg hydrocortisone and 1 mg dexamethasone = 25 mg hydrocortisone.
- Indicate whether the patient received an inhaled vasodilator in the last 24 hours by checking the appropriate "Yes/No" box on line 17. If "Yes," indicate which agent by checking the appropriate box and the date and time the current administration was started in the indicated field.
- Indicate if the patient received vasopressor support at any time since randomization by checking the appropriate "Yes/No" box on line 18. If "Yes," check the box next to each of the agents that was received, the highest infusion rate (and units) received, and the total hours receiving any vasopressor support. If "No" skip to question 19.
- . Indicate whether proning protocol was initiated or stopped in the prior 72 hours on line 19.
- Beginning on line 20, record the lowest and highest values for each indicated laboratory value since randomization. If there is only one value, record it in the lowest value field, and click the "Single" box. If there are no data, check the "None" box.
- If the patient was extubated prior to Study 7 skip to question 29.
- Indicate all ventilator modes used in the last 24 hours by checking the appropriate boxes under line 21 and circle the mode used at 0800.
- Indicate whether the patient was extubated in the last 24 hours by checking the appropriate "Yes/No" box on line 22 and, if extubated, enter the time and date in the appropriate fields.
- Record the highest and lowest measured tidal volumes in ml in the last 24 hours in the appropriate fields on line 23.
- Based on the EMR, estimate the total time in hours in the last 24 hours in which tidal volume exceeded 7 ml/kg and record in field on line 24.

- Enter the highest and lowest PEEP and Mean airway pressure in cm H_2O in the last 24 hours in the appropriate fields on lines 25 and 26, respectively.
- If still intubated between 0600 and 1000 on study day 7, record the plateau pressure and associated PEEP measured in this time interval in the indicated fields beginning on line 27. If multiple values are present, enter the value closest to 0800. If no values from that time period check the "No Values" box. If the patient was not intubated during this time period check the "Not intubated" box.
- If arterial blood gasses are performed, enter the highest and lowest PaO_2 and associated F_iO_2 since randomization in the appropriate fields on line 28. If only a single value enter the PaO_2 and F_iO_2 values in the "Lowest" field and check the "Single value" box. If no arterial blood gasses were performed, check the "None" box.
- Record total intake in ml in the field on line 29.
- Record the total output (including net volume removed by RRT) in the last 24 hours in the field on line 30.
- Indicate whether the research blood sample was collected by checking the appropriate "Yes/No" box on line 31.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 32.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 33.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 34.
- Indicate the location of the sample in the freezer and the displayed freezer temperature at the time the samples were placed in the indicated fields on line 35.

10.8/ Unassisted Breathing Checklist

- Complete one checklist for each "unassisted breathing (UAB)" period lasting ≥48 hours in the first 28 days after randomization.
- Enter name of individual entering information about start of ventilator-free period and the date/time ventilator-free period began (either extubation or, if on tracheostomy on trach collar) on line 1.
- Indicate whether a spontaneous breathing trial (SBT) was done prior to extubation/trach collar by checking the appropriate yes/no box on line 2.
- Indicate the mode used for the SBT, including the pressures in the appropriate fields on line 3.
- Enter duration of SBT in hours prior to extubation/trach collar in field on line 4.
- Complete the checklist beginning on line 5 by checking the appropriate "yes/no" boxes for questions 1-3 and 5-6. Indicate the value for the Rapid Shallow Breathing Index in the field for question 4.
- Indicate whether the patient remained UAB through study day 28 by checking the appropriate yes/no box on line 6. If "No," enter the date/time patient placed back on assisted breathing and the reason for ending UAB on line 7. UAB includes (1) spontaneously breathing with face mask, nasal prong oxygen including high flow, or room air; (2) T-tube

breathing; (3) tracheostomy mask breathing; (4) CPAP ≤5 cm H2O without PS or IMV assistance; or (5) use of CPAP or BIPAP solely for sleep apnea management.

- Calculate the number of study days in this UAB period that the patient was UAB for the entire study day (0800-0800). Note that assisted breathing administered for <24 hours solely to support surgery is not considered an interruption to continuous UAB. Enter the total number of ventilator-free (UAB) days in the indicated field on line 8.
- Enter name of person completing the checklist and the date and time it was completed on line 6.

10.9/ ICU Discharge CRF

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Complete one ICU discharge checklist each time an order is placed for ICU transfer.
- Record your name and the date and time the checklist is completed in the indicated fields on line 1.
- Enter the date and time of the EPIC order on line 2.
- Enter the date and time of actual transfer/discharge on line 3.
- Indicate the disposition (death or destination of ordered transfer/discharge) by checking the appropriate box on line 4.
- Indicate whether the patient was still receiving Assisted Breathing by checking the appropriate “Yes/No” box on line 5 and If “No,”, enter the date last received Assisted Breathing in the indicated field.
- Indicate whether the patient was receiving supplemental oxygen by checking the appropriate “Yes/No” box on line 6 and If “Yes,”, enter the type of delivery by checking the appropriate box and enter the flow rate or % oxygen delivered in the appropriate fields.
- Enter the results of the MOCA (points) on line 7.
- Indicate whether the discharge/transfer order was cancelled or the patient was readmitted to the ICU prior to study day 28 check the appropriate “Yes/No” box on line 8 and, if “Yes,” record the date and time of cancellation/readmission on line 9.
- Calculate the number of study days in this ICU-free period that the patient was ICU-free, including having an active transfer/discharge order and/or residing in a non-ICU setting, for the entire study day (0800-0800). Enter the total number of ICU-free days for this ICU-free period in the indicated field on line 10.
- Enter name of individual who completed data entry for the ICU-free period and date/time of completion in the appropriate fields on lane 11.
- For each readmission please use the subsequent ICU discharge checklist with the same instructions as above

10.10/ Day 28 Data CRF

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Record your name and the date and time CRF was completed in the indicated fields in line 1.

- Indicate if still alive by checking appropriate "Yes/No" box on line 2 and if "No" record date and time of death in the indicated fields on line 3 and check the box next to the most appropriate cause of death (from the discharge summary and discussion with the ICU provider team).
- Indicate whether patient has received any mechanical ventilation in the past 24 hours by checking the appropriate "Yes/No" box on line 4. If "No," record the date and time the patient last received mechanical ventilation in the appropriate fields.
- Indicate if patient is still in an ICU setting by checking the appropriate "Yes/No" box on line 5. If "No," record the date and time the patient was last in an ICU and check the box next to the best description of the patient's current location.
- Enter the total number of ventilator-free days in the first 28 days of the study on line 6:
    - If the patient is alive at day 28, enter the sum of ventilator-free days from all UAB periods recorded on the Unassisted Breathing CRF, otherwise enter 0.
- Enter the total number of ICU-free days in the first 28 days of the study on line 7:
    - If the patient is alive at day 28, enter the sum of ICU-free days from all ICU-free periods recorded on the ICU Discharge CRF, otherwise enter 0.

10.11/ Hospital Discharge CRF

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of the worksheet.
- Record your name and the date and time CRF was completed in the indicated fields in line 1.
- Enter date of hospital discharge in the indicated field on line 2.
- Indicate whether the patient was discharged from an ICU or an acute care unit by checking the appropriate box on line 3.
- Indicate the disposition (death or destination of ordered transfer/discharge) by checking the appropriate box on line 4.
- Indicate whether the patient was still receiving Assisted Breathing by checking the appropriate "Yes/No" box on line 5 and If "No,", enter the date last received Assisted Breathing in the indicated field on line 6.
- Indicate whether the patient was receiving supplemental oxygen by checking the appropriate "Yes/No" box on line 7 and If "Yes,", enter the type of delivery by checking the appropriate box and enter the flow rate or % oxygen delivered in the appropriate fields on line 8.
- Enter the results of the MOCA (points) on line 9.

10.12/ Adverse Event CRF

Refer to Section 12: Adverse Event Reporting

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of each page.
- Indicate on line 1 whether the patient had any adverse event (AE(by checking the appropriate "Yes/No" box.
- If "Yes,", fill out one column for each adverse event.

- In row 2 give a brief description of the AE.
- In row 3, record the name of the individual entering data about the AE.
- Record the date and time the AE was first detected in rows 4 and 5, respectively. If unknown, check the "?" box.
- Record the date and time the AE was resolved in rows 6 and 7, respectively. If unknown or if not resolved check the "?" box.
- Indicate the most appropriate severity grade of the AE by checking the appropriate box in row 8 (check only one box).
- Indicate whether the AE was serious by checking the appropriate "Yes/No" box in row 9.
- Indicate whether the AE was expected by checking the appropriate "Yes/No" box in row 10.
- Indicate likelihood of relatedness to the study intervention by checking the appropriate box in row 11 (check only one box).
- Indicate the action taking with the study intervention by checking the appropriate box in row 12 (check all that apply).
- Indicate other actions taken by checking the appropriate box in row 13 (check all that apply).
- Record the outcome by checking the most appropriate box in row 14 (check only one box).
- Enter the name of the investigator who made the assessment about severity and study relatedness in row 15.
- Enter the date of the assessment in row 16.

10.13/ 60-day follow-up

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of each page.
- If telephone contact was not made and the information was not otherwise collected, check the indicated box on line 1
- Fill out a row for each telephone contact attempted.
- Enter the date and time of the attempted contact in column 1 and 2.
- Indicate whether contact with patient or LAR occurred by checking the appropriate "Yes/No" box in column 4.
- If "No," indicate the action taken by checking the appropriate box in column 5.
- If contact was made, indicate if it was directly with the study patient by checking the appropriate "Yes/No" box on line 3.
- If "No," record the name of the contact person on line 3, their relationship with the study patient on line 4, and indicate if he contact person was the LAR by checking the appropriate "Yes/No" box on line 5.
- Answer question s about the patient's current level of functioning on lines 6-9 by checking the appropriate "Yes/No" box.
- Indicate the type of location in which the study patient currently resides by checking the appropriate box on line 10.
- Add any comments about the patient's level of function or alternative sources of information in the comment section.
- Record the name of individual completing the 60-day follow-up CRF and the date completed on line 11.

10.14/ 90-day follow-up

- Record site ID code, 3-digit study ID, and the unique 3 letter identifier in the indicated fields at the top of each page.
- If telephone contact was not made and the information was not otherwise collected, check the indicated box on line 1
- Fill out a row for each telephone contact attempted.
- Enter the date and time of the attempted contact in column 1 and 2.
- Indicate whether contact with patient or LAR occurred by checking the appropriate "Yes/No" box in column 4.
- If "No," indicate the action taken by checking the appropriate box in column 5.
- If contact was made, indicate if it was directly with the study patient by checking the appropriate "Yes/No" box on line 3.
- If "No," record the name of the contact person on line 3, their relationship with the study patient on line 4, and indicate if he contact person was the LAR by checking the appropriate "Yes/No" box on line 5.
- Answer question s about the patient's current level of functioning on lines 6-9 by checking the appropriate "Yes/No" box.
- Indicate the type of location in which the study patient currently resides by checking the appropriate box on line 10.
- Add any comments about the patient's level of function or alternative sources of information in the comment section.
- Record the name of individual completing the 90-day follow-up CRF and the date completed on line 11.

11./ Study Associated Risks and Risk Mitigation

a./ Although not expected to occur with modest TH to 34°-35°C, patients can develop:

b./ (1) persistent severe bradycardia (heart rate <30 associated with mean arterial pressure <65 without vasopressors); (2) uncontrolled bleeding and (3) intractable ventricular arrhythmias, there. In the event any of these conditions happens, TH protocol will be early terminated following clinical guidelines.

(4)There is a slightly Increased risk of infection, study subjects are closely monitored for infection and the appropriate use of antibiotics should be initiated as standard of care; (5) there is a mild risk of changes in fluid and chemical balance, this patient population is closely monitored and correction is implemented as standard of care; (5) there is a mild to moderate risk of hyperglycemia occur, this patient population is closely monitored and correction should be implemented as standard of care; (6) there is a slight reduction in the ability of blood clotting mechanism, this patient population is closely monitored and corrections should be implemented as standard of care.

12./ Adverse Event Reporting

Adverse events will be classified by according to the following definitions (21 CFR 312.32):

1. What is not an Adverse Event

Organ failures or death related to ARDS or the patient's underlying condition that are systematically captured by the protocol (primary or secondary outcomes) should not be reported as AEs unless they are considered study-related.

2. Severity

This is graded as Grade 1-5:

- Grade 1: Mild; asymptomatic or mild symptoms without need for intervention
- Grade 2: Moderate; symptomatic; minimal, local or noninvasive intervention indicated
- Grade 3: Severe; medically significant but not immediately life-threatening; prolongation of critical illness; disabling
- Grade 4: Life-threatening; urgent intervention indicated.
- Grade 5: Death related to AE

3. Serious

This will be reported as yes or no.

An AE will be classified as serious if it is fatal or immediately life-threatening (as the reaction occurred, not if it had occurred in a more serious form), permanently disabling, severely incapacitating, or requires or prolongs inpatient hospitalization. Events that may jeopardize the patient and require medical or surgical intervention to prevent one of the previously listed outcomes may also be classified as serious.

4. Unexpected

AEs will be classified as either expected or unexpected. An AE will be considered unexpected if it is not listed in the investigator brochure or protocol or not listed at the specificity or severity observed, or not consistent with the risk information described in the general investigational plan, or that in unexpected in the course of treatment for ARDS.

5. Study-related

AEs will be considered to be study-related if the event follows a temporal sequence from a study procedure and could have been produced by the study procedure. Study relatedness will be classified as follows:

1. Not related: not associated to the investigational procedure
2. Unlikely: unlikely to be associated to the investigational procedure
3. Possible: possibly associated to the investigational procedure
4. Probable: probably (>50% likelihood) associated to the investigational procedure
5. Definite: definitely associated to the investigational procedure

ii. Reporting requirements

The following will be reported to the IRB within 5 business days of the investigator becoming aware of the information:

1. Information that indicates a new or increased risk.
2. Any harm experienced by a subject or other individual which in the opinion of the investigator is **unexpected** and at least **probably related** to the investigation and places subjects or others at a greater risk of harm than was previously known or recognized.
3. Non-compliance with federal regulations governing human research, or with the requirements or determinations of the IRB, or allegations thereof.

4. Failure to follow the protocol due the action or inaction of the investigator or research staff
5. Breach of confidentiality
6. Change to the protocol with prior notification of the IRB to avoid an immediate hazard to a research subject
7. Incarceration of a subject in a study not approved by the IRB to include prisoners
8. Complaint of a subject or authorized representative that cannot be resolved by the research team.
9. Suspension or termination of the research by the sponsor or the investigator.
10. Unanticipated adverse device effect

Any deaths or life-threatening events temporally related with study procedures, including cooling and rewarming, and unexpected SAEs will be reviewed by Dr. Hasday based on information provided by Dr. Shanholtz. Dr. Hasday will report the SAE, including his assessment of relatedness to study procedures, to the UMB IRB and the Dr. Verceles within 48 hours of discovery. All other AEs will be tabulated without case-by-case review unless a difference between treatment groups calls for review of a group of cases. Dr. Terrin will submit monthly tabular reports of all SAEs/RAEs to Dr. Verceles and will submit tabular summaries of all AEs to Dr. Verceles every 6 months.

13./ Sample Collection and Processing:

The COVID-CHILL-pilot Study Coordinator, the CHILL-pilot PI's or other CHILL-pilot Clinical Team members will be responsible for sample collection, handling, and transport to Dr. Hasday's research laboratory for processing a storage. A kit will be provided for each subject, which will contain pre-printed labels containing the 2-digit site number, 3-digit subject number, and 2-digit study day number and 1.5 ml cryotubes pre-labeled the 2-digit site number, 3-digit subject number, 2-digit study day number and aliquot identification (a-g). Twelve milliliters EDTA-anticoagulated blood will be collected in two purple-top Vacutainer™ tubes at baseline on each of study days 1-4 and 7 and will be transported on ice to the Hasday laboratory for processing and storage within 60 minutes of collection. The blood will be centrifuged at 1000 g at 4°C for 5 minutes and plasma collected and 0.5 ml aliquots transferred to the prelabeled cryotubes. The samples will be entered into an Excel database with information about sample identification, number of aliquots, name of person that collected and processed the samples, date and time of processing, location in the -80°C freezer, and any comments about deviation in the processing protocol. Samples will be place in 2" high freezer boxes and placed in a remotely-monitored -80°C freezer with liquid CO_2 back-up in the Hasday lab in Health Science Facility-II.

Data Management

Data management will be performed by the DC using standard operating procedures (SOPs) developed by the DC in consultation with the CC using paper CRFs. CC clinical staff (Drs. Hasday and Shanholtz, the COVID-CHILL-pilot Study Coordinator, and Clinical Team members) will collect data on CRFs with source documents to be maintained securely in the CHILL-pilot Study Coordinator's office.

APPENDIX

CHILL Pilot Case Report Forms:

1. Screening, Enrollment, Randomization CRF
2. Baseline Data CRF
3. Day 1 Data CRF
4. Day 2 Data CRF
5. Day 3 Data CRF
6. Day 4 Data CRF
7. Day 7 Data CRF
8. Unassisted Breathing CRF
9. IDU Discharge CRF
10. Day 28 CRF
11. Hospital Discharge CRF
12. Adverse Event Report CRF
13. 60-day Follow-up CRF
14. 90-day Follow-up CRF
15. Patient Disposition CRF

Screening/Enrollment/Randomization Source Document

Obtain screening number and complete this form for all patients 18-65 years old with a confirmed COVID-19 diagnosis, intubated or trached and ventilated for < 7 days.

[1]Screening Completed by _____

[2]Date/Time of Initial Screen: ☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[3]Type of Unit: ☐ Medical ☐ Surgical ☐ Med/Surg ☐ Trauma ☐ ED

[4]Gender (at birth): ☐ Male ☐ Female [5]Date of Birth: ☐☐/☐☐/☐☐☐☐
MONTH D D Y Y Y Y

[6]**Ethnicity**: ☐ Hispanic or Latino ☐Not Hispanic or Latino

[7]**Race:** Asian:☐Yes ☐No Native Hawaiian/Pacific Islander:☐Yes ☐No White:☐Yes ☐No
Black/African American:☐Yes ☐No American Indian/Alaskan Native:☐Yes ☐No
Not reported:☐Yes ☐No

[8]Date first positive SARS-CoV-2 test ☐☐/☐☐/☐☐☐☐
MONTH D D Y Y Y Y

[9]If subject meets any of the following exclusion criteria, they are excluded and you can STOP here and complete the screening log entry, otherwise proceed to Berlin criteria checklist./

☐ Moderate-severe ARDS (bilateral infiltrates and P/F < 200) present for >48hrs
☐ Missed NMB window: (>12 hrs)
☐ Missed mechanical ventilation window (>7 days)
☐ Refractory hypotension (> 0.2 mcg/kg/min of NE or equivalent dose for a minimum of 6 h)
☐ Core temperature <35.5°C while not receiving CRRT
☐ No Legally authorized representative
☐ Significant, active bleeding
☐ Platelets <10K (uncorrected)
☐ Active hematologic malignancy
☐ Skin process precludes cooling device
☐ Moribund, not likely to survive 72h
☐ Pre-morbid condition makes it unlikely that patient will survive 28 days
☐ Do Not Resuscitate status
☐ Not likely to remain intubated for ≥48h
☐ Physician unwilling to participate
☐ Severe underlying lung disease
  ☐ On home O2
  ☐ On BIPAP (except for OSA)
  ☐ prior lung transplantation
☐ BMI >45
☐ Known NYHA class IV heart disease
☐ Acute Coronary Syndrome (MI, unstable angina)
☐ Cardiac arrest within 30 days of enrollment
☐ Burns over >20% of the body surface
☐ Previously randomized in CHILL study
☐ Severe chronic liver disease (Child-Pugh score of 12-15)[6]Berlin Criteria checklist:

[10]Starting from the first ventilator day, answer questions until patient is enrolled and randomized or exceeded 7 ventilator days. For each day record the date/time of the first positive study.

Vent Day	Chest x-ray or CT performed	Bilateral infiltrates	NOT fully cardiogenic	Date/time of study
1	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)
2	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)
3	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)
4	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)
5	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)
6	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)
7	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	MONTH / D D / Y Y Y Y TIME (0-2400)

[11]Meets Berlin ARDS mechanical ventilation and bilateral infiltrates not fully cardiogenic and no exclusion factors (refer to checklist)?//

///☐Yes Offer enrollment and proceed to next question

☐No STOP

[12]Did Patient (or LAR) give consent?

///☐Yes Go P/F ratio table

☐No STOP

[13]P/F Ratio Table.

Vent day	PEEP≥8 cm H_2O	P/F ratio <200	Measured (M) or Inferred (I)	Value*	Date/Time
1	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)
2	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)
3	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)
4	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)
5	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)
6	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)
7	☐ Yes ☐ No	☐ Yes ☐ No	☐ M ☐ I	☐☐☐	MONTH / D D / Y Y Y Y TIME (0-2400)

*For inferred P/F, record second (confirming) value.

eTable 2: Imputed PF ratio (cells) for combinations of SpO_2 (rows) and FiO_2 (columns)

	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

Conditions required to use inferred P/F ratio include: (a) SpO2 values 80-96%, (b) SpO_2 measured ≥10 min after F_IO_2 change, (c) PEEP ≥ 8 cm H_2O, (d) adequate pulse oximeter wave form, and (e) qualifying inferred P/F ratio is confirmed 1-6 hrs after the initial determination.

[14]P/F ratio criterion met within 7 ventilator days

☐ Yes Collect baseline blood sample, randomize and record randomization time and treatment assignment below

☐ No STOP

[15]Is this patient currently receiving prone positioning alternating with supine positioning?

☐ Yes

☐ No

[16]Randomization date/time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐

MONTH D D Y Y Y Y TIME (0-2400)

[17]Treatment assignment (check one)

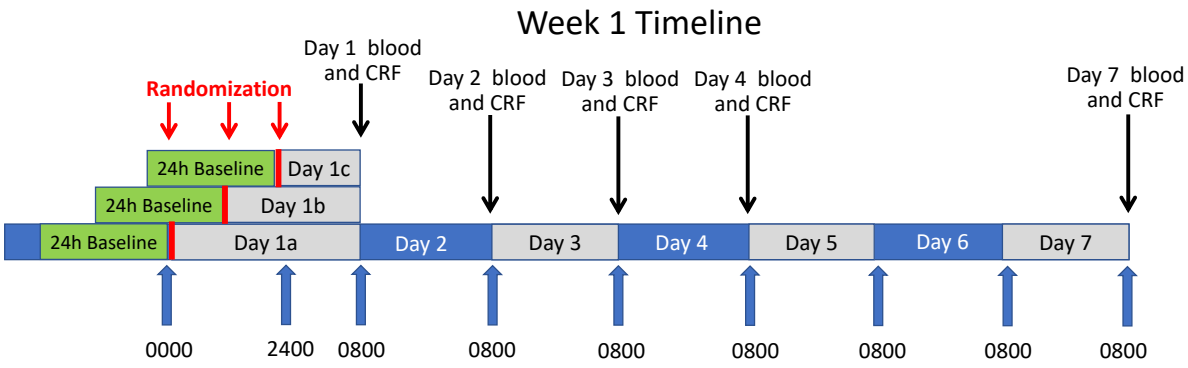
☐ Therapeutic Hypothermia

☐ Usual Treatment

Initiate sedation, NMB, and cooling protocol for subjects randomized to Therapeutic Hypothermia

Complete Baseline information CRF.

See schedule for first week blood and data collection below.



- Collect baseline blood and complete Baseline CRF based on 24h preceding randomization
- Collect day 1 blood and complete Day 1 CRF at 0800 on randomization day + 1; (the duration of day 1 may be 8h 1 min to 31h 59 min as indicated by the examples a - c)
- Collect blood and complete CRFs for Day 2, 3, 4, and 7 at 0800 on randomization day + 2, +3, +4, and +7 covering the prior 24h period

BASELINE DATA

[1]Form Completed by _____ MONTH / D D / Y Y TIME (0-

[2]Hospital admission date: MONTH / D D / Y Y Y Y

[3]Type of ICU: ☐ Medical ☐Surgical ☐ Trauma ☐ Med/Surg ☐ Burn ☐ Neuro

[4]ICU admission Date/Time: MONTH / D D / Y Y Y Y TIME (0-2400)

[5]Patient admitted to ICU from: ☐ OR ☐ Another special care unit ☐ Floor
☐ Recovery room ☐ Another hospital ☐ Stepdown unit
☐ ER ☐ Direct admission

[6]What was patient's pre-admission level of independence?
☐ Living independently
☐ Home with help
☐ Home with professional help (nursing)
☐ Intermediate care or rehab facility
☐ Skilled nursing facility
☐ Other _____

[7]Smoking status:
☐ Never smoker
☐ Current smoker ☐☐ Peak pack-years
☐ Former smoker ☐☐ Peak pack-years Quit date MONTH / Y Y Y Y

[8]Has the patient had surgery within the last week? ☐Yes ☐No Date: MONTH / Y Y Y Y
If No skip to question #9.

Type of procedure (Check all that apply):
☐ Abdominal ☐ Thoracic/lung ☐ Cardiac ☐ Orthopedic ☐ Vascular ☐ Neuro
☐ Urologic ☐ OB/Gyn ☐ Plastic ☐ ENT/Craniofacial ☐ Breast

[9]Chronic health information available:

Chronic peritoneal or hemodialysis	☐ Yes ☐ No
CKD Stage III-V	☐ Yes ☐ No
HIV+ with AIDS criteria)	☐ Yes ☐ No
Solid tumor with metastasis	☐ Yes ☐ No
Immune suppression (radiation, chemotherapy, ≥0.3 mg/kg/day prednisone) in last 6 months:	☐ Yes ☐ No
Hepatic failure with coma/encephalopathy:	☐ Yes ☐ No
Heart failure NYHA II-III :	☐ Yes ☐ No
Pulmonary Hypertension:	☐ Yes ☐ No

Additional Past Medical History:
Diabetes Mellitus: ☐ Yes ☐ No (Type ☐1 ☐2) Interstitial lung disease: ☐ Yes ☐ No
COPD: ☐ Yes ☐ No Asthma: ☐ Yes ☐ No Atherosclerotic Disease ☐ Yes ☐ No

USE VALUES FROM 24 HRS PRECEDING RANDOMIZATION

If no values were obtained for clinical purposes during 24 hours preceding randomization, **the lab tests must be obtained after consent and before study procedures.**

If only single temperature measurement in last 24 hours, record in "Lowest" field and check "Single" box. If no temperature measurements check "None box.

[10]Temperature: Lowest ☐☐.☐ °C Highest: ☐☐.☐ °C Single ☐ None ☐

Site of temperature measurement: ☐ Esophageal ☐ Bladder ☐ CVC ☐ Peripheral

[11]Systolic BP: Lowest ☐☐☐ Highest ☐☐☐ mm Hg Single ☐

Mean arterial pressure: Lowest ☐☐☐ Highest ☐☐☐ mm Hg Single ☐

Heart rate: Lowest ☐☐☐ Highest ☐☐☐ beats/min Single ☐

Respiratory rate: Lowest ☐☐☐ Highest ☐☐☐ breaths/min Single ☐

[12]Was patient mechanically ventilated when the lowest respiratory rate occurred? ☐ Yes ☐ No

[13]Urine output for 24 hrs preceding randomization: ☐☐☐☐☐ ml

Total output for 24 hrs pre-randomization: ☐☐☐☐☐ ml (includes negative CRRT balance)

Total intake for 24 hrs pre-randomization: ☐☐☐☐☐ ml

Was Intake/Output data for 24 hours? ☐Yes ☐No If <24 hours, how many hours: ☐☐.☐

[14]**<u>Laboratory data (if only one value, record in "Lowest" field and click "Single" box; if no data, click "None" box)</u>:**

<u>CBC values</u>:

WBC:	Lowest: ☐☐.☐	Highest: ☐☐.☐	x1000/mm^3	Single ☐	None ☐
Hgb	Lowest: ☐☐.☐	Highest: ☐☐.☐	g/dL	Single ☐	None ☐
Hct:	Lowest ☐☐.☐	Highest: ☐☐.☐	%	Single ☐	None ☐
Platelets:	Lowest: ☐☐☐	x1000/mm^3			None ☐

<u>Serum Levels</u>:

Sodium	Lowest: ☐☐☐	Highest: ☐☐☐	mEq/L	Single ☐	None ☐
Potassium:	Lowest: ☐.☐	Highest: ☐.☐	mEq/L	Single ☐	None ☐
Bicarbonate:	Lowest: ☐☐.☐	Highest: ☐☐.☐	mEq/dL	Single ☐	None ☐
BUN:	Lowest: ☐☐.☐	Highest: ☐☐.☐	mg/dL	Single ☐	None ☐
Creatinine:	Lowest: ☐☐.☐☐	Highest: ☐☐.☐☐	mg/dL	Single ☐	None ☐
Glucose:	Lowest: ☐☐☐	Highest: ☐☐☐	mg/dL	Single ☐	None ☐
Magnesium:	Lowest: ☐.☐	Highest: ☐.☐	mmol/L	Single ☐	None ☐
Phosphate	Lowest: ☐.☐	Highest: ☐.☐	mg/dL	Single ☐	None ☐
Albumin:	Lowest: ☐.☐	Highest: ☐.☐	g/dL	Single ☐	None ☐
Bilirubin:	Lowest: ☐☐.☐	Highest: ☐☐.☐	mg/dL	Single ☐	None ☐

Highest AST ☐☐☐ U/L None ☐ Highest ALT ☐☐☐ U/L None ☐

Respiratory Parameters:

[15] For the 24 hours preceding randomization, record the lowest measured post-intubation SpO_2 date and time of measurement, and the Mean Airway Pressure, measured PEEP, and FiO_2 from the nearest time relative to the lowest SpO_2 measurement. Record the post-intubation ABG with the lowest PaO_2, the date and time that the ABG sample was collected and the Mean Airway Pressure, and FiO_2 measured PEEP from the nearest time relative to that ABG. If no ABGs were done, check the None box.

SpO_2: Lowest SpO_2: ☐☐☐ %

Date/Time of SpO_2 measurement: ☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

Corresponding Mean Airway Pressure: ☐☐ cm H_2O

Corresponding Measured PEEP: ☐☐ cm H_2O

Corresponding FiO_2: ☐☐☐ %

ABG: Lowest PaO_2: ☐☐☐ mm Hg

pH: ☐.☐☐ pCO_2: ☐☐☐ mm Hg

Date/Time of ABG collection: ☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

Corresponding Mean Airway Pressure: ☐☐ cm H_2O

Corresponding Measured PEEP: ☐☐ cm H_2O

Corresponding FiO_2: ☐☐ %

None ☐

Ventilator Settings (record most recent values prior to randomization)

[16]**Date/Time of recorded settings:** ☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[17]**Ventilator/ Mode**

☐ **DRAEGER**

☐PC-CMV	☐VC-CMV	☐SPN-CPAP/PS
☐PC-AC	☐VC-AC	☐SPN-CPAP/VS
☐PC-SIMV	☐VC-SIMV	☐SPN-PPS
☐PC-BIPAP	☐VC-MMV	☐SPN-CPAP
☐PC-APRV		
☐PC-HFO		
☐PC-MMV		

☐**SERVO**

☐VC-AC	☐BiVent
☐PC-AC	☐PS
☐PRVC	☐VS
☐VC-SIMV	☐CPAP
☐PC-SIMV	☐NIV
☐PRVC-SIMV	
☐ **Other**_____	

[18]For **volume targeted modes**: Set tidal volume: ☐☐☐☐ ml

[19]For **pressure control/dual mode:** Inspiratory Time: ☐.☐☐ sec; Pressure ☐☐ cm H_2O

[20]Set rate: ☐☐ breaths/min PEEP ☐☐ cm H_2O

[21]If APRV/BiVENT: $P_{1/high}$ ☐☐ cm H_2O $P_{2/PEEP}$ ☐☐ cm H_2O $T_{1/high}$ ☐.☐ sec

$T_{2/PEEP}$ ☐.☐ sec

[22]**Measured Parameters (most recent values recorded in EMR prior to randomization):**

Tidal volume: ☐☐☐☐ ml Respiratory rate: ☐☐ breaths/min

Minute ventilation: ☐☐.☐ L/min

SpO2: ☐☐☐ % Plateau pressure: ☐☐ cm H_2O (at PEEP and FiO_2 recorded above)

Peak Inspiratory pressure: ☐☐ cm H_2O Mean airway pressure: ☐☐ cm H_2O

I:E ratio ☐.☐

[23]**ARDSnet Guideline Checklist (at randomization):**

Is tidal volume 5-7 ml/kg IBW? ☐Yes ☐No

Is plateau pressure ≤ 30 cm H_2O?: ☐Yes ☐No

Is SpO_2 between 88 and 95%? ☐Yes ☐No

Is RR < 35 BPM? ☐Yes ☐No

Is I:E ratio between 1:1 and 1:3? ☐Yes ☐No

If **NO**, ask respiratory therapist to adjust ventilator parameters to try to meet goals (might not be achievable). Date/Time of change: ☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[24]**Post-change measurements**:

Tidal Volume: ☐☐☐☐ ml Plateau Pressure*: ☐☐ cm H_2O PEEP: ☐☐ cm H_2O

*Plateau pressure or equivalent (Peak Inspiratory Pressure on PS/PC, $P_{1/high}$ on APRB/BiVent)

[25]**Vital signs (most recently recorded prior to randomization)**

Measured Height: ☐☐☐ cm and weight: ☐☐☐.☐ kg Predicted weight: ☐☐☐.☐ kg

Heart rate: ☐☐☐ beats/min SBP/DBP/MAP: ☐☐☐ / ☐☐☐ / ☐☐☐ mm Hg

CVP: ☐☐ cm H_2O No CVP ☐ Temperature °C ☐☐.☐ Site: ☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV

[26]**Vasopressor support in 24h prior randomization** ☐Yes ☐No (if No skip to line 27)
(check all received and highest infusion rate for each):

- ☐ Dobutamine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
- ☐ Dopamine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
- ☐ Norepinephrine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
- ☐ Epinephrine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
- ☐ Vasopressin ☐☐.☐☐ units/min
- ☐ Phenylephrine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
- ☐ Milrinone ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min

Total hours receiving vasopressor support: ☐☐

[27]Is patient on inhaled vasodilator?: ☐Yes ☐No (if No skip to line 29)

[28]Start Date/Time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

☐Epoprostenol ☐Nitric Oxide

[29]Is patient receiving corticosteroids: ☐Yes ☐No (If No skip to line 30).

Total hydrocortisone equivalent dose (over past 24 hrs): ☐☐☐ mg

1 mg prednisone or methylprednisolone = 4 mg hydrocortisone

1 mg dexamethasone = 25 mg hydrocortisone

[30]Other COVID treatments: ☐None _____ _____ _____

_____ _____ _____ _____

[31]Date/Time NMB was started: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[32]If proning protocol initiated, Date/Time proning protocol initiated: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[33]**If in hypothermia group, Date/Time cooling was initiated:** ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[34]Cooling method(s) used:
☐Blanketrol cooling blanket ☐Artic Sun ☐Gaymar ☐Ice packs

[35]**Research blood sample collected:** ☐ Yes ☐No

[36]Blood collected: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ Processed: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400) MONTH D D Y Y Y Y TIME (0-2400)

[37]Number 0.5 ml aliquots: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

[38]Date/Time placed in -80°C freezer: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[39]Location in freezer: _____ Temperature reading on freezer: -☐☐ °C

Enter Contact information (for 60- and 90-day follow-up):

Patient:
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Legally Authorized Representative (Name): _____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Additional Contact 1: Name:_____ Relationship to patient:_____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Additional Contact 2: Name:_____ Relationship to patient:_____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Additional Contact 3: Name:_____ Relationship to patient:_____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Additional Contact 4: Name:_____ Relationship to patient:_____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Additional Contact 5: Name:_____ Relationship to patient:_____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

Additional Contact 6: Name:_____ Relationship to patient:_____
Home Phone: ___-___-____ Cell: ___-___-____
Email:_____

DAILY DATA – Day 01

(To be completed as close to 0800 as possible on the day after randomization)

[1]Form Completed by _____ MONTH / D D / Y TIME (0-

[2]Vital status ☐ Alive ☐ Dead (If alive, skip to line 5)

[3]Time of death: MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Cause of death (from discharge summary/discussion with ICU team), then skip to question 11.

☐ Respiratory failure ☐ Cardiac (arrhythmia, ACS, cardiogenic shock) ☐ Multi-organ failure

☐ Refractory shock ☐ Intraabdominal (perforation, compartment) ☐ Withdrawal of care

☐ Neurological devastation ☐ Severe sepsis ☐ Refractory acidosis ☐ Hemorrhage

[5]Is patient still receiving NMB? ☐ Yes ☐ No If "Yes" skip to question 9

[6]Date/Time NMB discontinued: MONTH / D D / Y Y Y Y TIME (0-2400)

[7]Reason for discontinuation: ☐ Refractory bradycardia ☐ Possible drug reaction ☐ Decision of ICU provider ☐ Decision of family

[8]Date/Time: neuromuscular function (4 twitches/TOF) returned: MONTH / D D / Y Y Y Y TIME (0-2400)
or ☐Did not return

[9]Is patient in hypothermia group? ☐ Yes ☐ No **If "No" skip to question 14**

[10]Minutes to reach 35°C from randomization: ___ from initiation of cooling: ___

[11]Still being cooled? ☐ Yes ☐ No If **"Yes" skip to question 15**

[12]If No, when was cooling stopped? MONTH / D D / Y Y Y Y TIME (0-2400)

[13]Reason for discontinuation: ☐ Refractory bradycardia with hypotension ☐ Hemorrhage ☐ Intractable ventricular arrhythmia ☐ Decision of ICU provider ☐ Decision of family

Skip to question 15.

[14]If in the Control arm, received therapeutic hypothermia in last 24 hrs? ☐ Yes ☐ No ☐ N/A

[15]Still intubated or receiving Assisted Breathing? ☐ Yes ☐ No ☐ N/A

If "No," when was patient extubated or UAB for ≥48 hours? MONTH / D D / Y Y Y Y TIME (0-2400)

[16]Was RRT started since randomization? ☐ Yes ☐ No ☐ N/A

[17]If RRT had been previously initiated has it stopped since randomization? ☐Yes ☐No ☐N/A

[18]Since randomization did the patient have any of the following:

Bradycardia (with mean arterial pressure < 65 mm Hg or needing pressors) ☐ Yes ☐ No

Significant Bleeding (Required IR, Surgery or >3u pRBCs) ☐Yes ☐No

Diagnosis of new pneumonia ☐ Yes ☐ No

[19]**Vital signs (Record highest and lowest values since randomization; If only one value, record as lowest and check the "Single" box.**

Systolic BP: Lowest: ___ Highest: ___ mm Hg Single ☐

Diastolic BP: Lowest: ___ Highest: ___ mm Hg Single ☐

CVP: Lowest: ___ Highest: ___ cm H_2O CVP not available ☐ Single ☐

Mean arterial pressure: Lowest: ___ Highest: ___ mm Hg Single ☐

[20]Record date MONTH / D D / Y Y Y Y **and time** TIME (0-2400) **of randomization**

Check box in first column of table below indicating randomization time.

Record date MONTH / D D / Y Y Y Y **and time** TIME (0-2400) **cooling started or check Not Cooled** ☐

[21]For each 2 hr block from randomization until 0800 of DAY AFTER randomization record highest and lowest temperature and lowest SpO_2 and the FiO_2 and Mean Airway Pressure measured closest to the SpO_2 reading. If only one temperature measurement for block, enter in "Low" field and check box. If no SpO_2 value for block, check "None" box.

Check box indicating randomiz-ation time	Time period	Temp (°C) If only one value record as "Low" and check box	Site of Temp measurement	Low SpO_2 (%)*	FiO2 (%)	Mean airway pressure (cm H_2O)
Day of Randomization						
☐/	0001 to 0200	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	0201 to 0400	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	0401 to 0600	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	0601 to 0800	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	0801 to 1000	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	1001 to 1200	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	1201 to 1400	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	1401 to 1600	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	1601 to 1800	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	1801 to 2000	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	2001 to 2200	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
☐	2201 to 2400	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
	0001 to 0200	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
	0201 to 0400	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
	0401 to 0600	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		
	0601- to 0800	High: Low: ☐	☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV	None ☐		

Since randomization did patient receive?

[22]**Corticosteroid**: ☐Yes ☐No If yes, total daily dose (prednisone equivalent): ☐☐☐ mg

1 mg prednisone/methylprednisolone = 4 mg hydrocortisone; 1 mg dexamethasone = 25 mg hydrocortisone

[23]**Inhaled vasodilator:** ☐Yes ☐No If "Yes": indicate agent(s) used and total hrs administered

☐Epoprostenol ☐Nitric Oxide Total hours administered: ☐☐

[24]**Vasopressor support since randomization** ☐Yes ☐No **If No proceed to question 25. (check all received and highest infusion rate for each):**

☐ Dobutamine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

☐ Dopamine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

☐ Norepinephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

☐ Epinephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

☐ Vasopressin ☐☐.☐☐ units/min

☐ Phenylephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

☐ Milrinone ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

Total hours receiving vasopressor support: ☐☐

[25]**Laboratory data (if only one value, record in "Lowest" field and click "Single" box; if no data, click "None" box):**

CBC values:

WBC:	Lowest: ☐☐☐	Highest: ☐☐☐	x1000/mm^3	Single ☐	None ☐
Hgb:	Lowest: ☐☐☐	Highest: ☐☐☐	g/dL	Single ☐	None ☐
Hct:	Lowest: ☐☐☐	Highest: ☐☐☐	%	Single ☐	None ☐
Platelets:	Lowest: ☐☐☐	x1000/mm^3			None ☐

Serum Levels:

Potassium:	Lowest: ☐.☐	Highest: ☐.☐	mEq/L	Single ☐	None ☐
Bicarbonate:	Lowest: ☐☐.☐	Highest: ☐☐.☐	mEq/dL	Single ☐	None ☐
BUN:	Lowest: ☐☐.☐	Highest: ☐☐.☐	mg/dL	Single ☐	None ☐
Creatinine:	Lowest: ☐☐.☐☐	Highest: ☐☐.☐☐	mg/dL	Single ☐	None ☐
Glucose:	Lowest: ☐☐☐	Highest: ☐☐☐	mg/dL	Single ☐	None ☐
Magnesium:	Lowest: ☐.☐	Highest: ☐.☐	mmol/L	Single ☐	None ☐
Phosphate	Lowest: ☐.☐	Highest: ☐.☐	mg/dL	Single ☐	None ☐
Albumin:	Lowest: ☐.☐	Highest: ☐.☐	g/dL	Single ☐	None ☐
Bilirubin:	Lowest: ☐☐.☐	Highest: ☐☐.☐	mg/dL	Single ☐	None ☐

Highest AST: ☐☐☐☐ U/L None ☐ Highest ALT: ☐☐☐☐ U/L None ☐

[26]**Highest/Lowest finger stick glucose every 6 hrs randomization through 0600 the next day (if only single value, enter in "Lowest" field and check "Single value" box; If no data, check "None" box:**

Time Period	Lowest Glucose (mg/dL)	Highest Glucose (mg/dL)	Single value	None
Day of Randomization				
0001-600				
0601-1200				
1201-1800				
1801-2400				
0001-600				

[27]**Ventilator mode/parameters used since randomization:**
(check all that apply, circle the current one)

☐ **DRAEGER**

☐PC-CMV ☐VC-CMV ☐SPN-CPAP/PS
☐PC-AC ☐VC-AC ☐SPN-CPAP/VS
☐PC-SIMV ☐VC-SIMV ☐SPN-PPS
☐PC-BIPAP ☐VC-MMV ☐SPN-CPAP
☐PC-APRV
☐PC-HFO
☐PC-MMV
☐Other _____

☐**SERVO**

☐VC-AC ☐BiVent
☐PC-AC ☐PS
☐PRVC ☐VS
☐VC-SIMV ☐CPAP
☐PC-SIMV ☐NIV
☐PRVC-SIMV

[28]**Extubated:** ☐ Yes ☐ No If Yes, Date/Time of extubation: ☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

ARDSNet Ventilation Adherence Data (if still intubated and mechanically ventilated):

[29]Measured Tidal Volumes: Lowest: ☐☐☐☐ ml Highest: ☐☐☐☐ ml

[30]Estimated hours patient ventilated with tidal volume **> 7 ml/kg** ☐☐.☐ hrs

[31]Applied PEEP: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

[32]Mean airway pressure: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

Lung Physiology Parameters (recorded 0600-1000 day 1 post-randomization; If no data available, check "No values" box. If patient not intubated, check "Not intubated" box)

[33]Plateau Pressure: ☐☐ cm H_2O and associated PEEP: ☐☐ cm H_2O.

No values: ☐ Not intubated: ☐

Arterial Blood Gas (if only one value, record in "Lowest" field and check "Single value" box. If no ABG data check "None" box)

[34]PaO_2 /FiO_2: Lowest: ☐☐☐ mm Hg/☐☐☐ % Highest: ☐☐☐ mm Hg/☐☐☐ % mm Hg

Single Value: ☐ None: ☐

Fluid Management:

[35]Total Intake since randomization: ☐☐☐☐☐ mL

[36]Total Output since randomization (include dialysis/CRRT): ☐☐☐☐☐ mL

[37]**Plasma sample collected:** ☐ Yes ☐No

[38]Blood collected: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ Processed: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400) MONTH D D Y Y Y Y TIME (0-2400)

[39]Number 0.5 ml aliquots: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

[40]Date/Time placed in -80°C freezer: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[41]Location in freezer: _____ Temperature reading on freezer: °C -☐☐

DAILY DATA – Day 03

(to be obtained as close to 0800 as possible on day 2 after randomization)

[1]Form Completed by _____ MONTH / D D / Y Y Y Y TIME (0-2400)

[2]Vital status ☐ Alive ☐ Dead

[3]If Dead Date/Time of death: MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Cause of death (from discharge summary/discussion with ICU team), then skip to question 11.

☐ Respiratory failure ☐ Cardiac (arrhythmia, ACS, cardiogenic shock) ☐ Multi-organ failure

☐ Refractory shock ☐ Intraabdominal (perforation, compartment) ☐ Withdrawal of care

☐ Neurological devastation ☐ Severe sepsis ☐ Refractory acidosis ☐ Hemorrhage

[5]Still receiving NMB? ☐ Yes ☐ No

If No and discontinued in last 24 hrs, answer following questions:

[6]Date/Time discontinued: MONTH / D D / Y Y Y Y TIME (0-2400)

[7]Reason for discontinuation: ☐ Refractory bradycardia ☐ Possible drug reaction

☐ Decision of ICU provider ☐ Decision of family ☐ As per Study protocol

[8]Date/Time: neuromuscular function (4 twitches/TOF) returned: MONTH / D D / Y Y Y Y TIME (0-2400)

or ☐Did not return

[9]Is patient in hypothermia group? ☐ Yes ☐ No **If "No" skip to question 13**

[10]Still being cooled? ☐ Yes ☐ No **If "Yes" skip to question 14**

[11]If No, when was cooling stopped? MONTH / D D / Y Y Y Y TIME (0-2400)

[12]Reason for discontinuation: ☐ Refractory bradycardia with hypotension ☐ Hemorrhage

☐ Intractable ventricular arrhythmia ☐ Decision of ICU provider ☐ Decision of family

Skip to question 14.

[13]If in the Control arm, received therapeutic hypothermia in last 24 hrs? ☐ Yes ☐ No ☐ N/A

[14]Still intubated or receiving Assisted Breathing? ☐ Yes ☐ No ☐ N/A

If No, when was patient extubated or UAB for ≤48 hours? MONTH / D D / Y Y Y Y TIME (0-2400)

[15]Was RRT started in last 24 hrs? ☐ Yes ☐ No ☐ N/A

[16]If RRT had been previously initiated has it stopped since randomization? ☐Yes ☐No ☐N/A

[17]In the last 24 hrs did the patient have any of the following:

Bradycardia (with mean arterial pressure < 65 mm Hg or needing pressors) ☐ Yes ☐ No

Significant Bleeding (Required IR, Surgery or >3u pRBCs) ☐Yes ☐No

Diagnosis of new pneumonia ☐ Yes ☐ No

[18]**Vital signs in last 24 hrs**

Systolic BP: Lowest: ___ Highest: ___ mm Hg Single ☐

Diastolic BP: Lowest: ___ Highest: ___ mm Hg Single ☐

CVP: Lowest: ___ Highest: ___ cm H_2O CVP not available ☐ Single ☐

Mean arterial pressure: Lowest: ___ Highest: ___ mm Hg Single ☐

[19]For each 2 hr block for the last 24 hrs record highest and lowest temperature and lowest SpO_2 and the FiO_2 and Mean Airway Pressure measured closest to the SpO_2 reading. If only single temperature measurement for block, check "Single value" box. If no SpO_2 measured for block, check the "None" box.

Time period	Temp (°C) If only one value record as "Low" and check box	Site of Temp measurement	Low SpO_2 (%)*	FiO2 (%)	Mean airway pressure (cm H_2O)
0801 to 1000	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1001 to 1200	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1201 to 1400	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1401 to 1600	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1601 to 1800	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1801 to 2000	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
2001 to 2200	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
2201 to 2400	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0001 to 0200	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0201 to 0400	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0401 to 0600	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0601- to 0800	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			

In last 24 hours did patient receive?

[20]**Corticosteroid**: ☐Yes ☐No If yes, total daily dose (prednisone equivalent): ☐☐☐ mg

1 mg prednisone/methylprednisolone = 4 mg hydrocortisone; 1 mg dexamethasone = 25 mg hydrocortisone

[21]**Inhaled vasodilator:** ☐Yes ☐No If "Yes": indicate agent(s) used and total hrs administered

☐Epoprostenol ☐Nitric Oxide Total hours administered: ☐☐

[22]**Vasopressor support in last 24 hrs** ☐Yes ☐No **If No proceed to question 23**. **(check all received and highest infusion rate for each):**

☐ Dobutamine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Dopamine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Norepinephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Epinephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Vasopressin ☐☐.☐☐ units/min
☐ Phenylephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Milrinone ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

Total hours receiving vasopressor support: ☐☐

[23]Did the patient start proning ☐Yes ☐No or stop proning ☐Yes ☐No in the last 24 hours?

[24] **Laboratory data (if only one value, record in "Lowest" field and click "Single" box; if no data, click "None" box):**

CBC values:

WBC: Lowest: ☐☐☐ Highest: ☐☐☐ x1000/mm^3 Single ☐ None ☐
Hgb: Lowest: ☐☐☐ Highest: ☐☐☐ g/dL Single ☐ None ☐
Hct: Lowest: ☐☐☐ Highest: ☐☐☐ % Single ☐ None ☐
Platelets: Lowest: ☐☐☐ x1000/mm^3 None ☐

Serum Levels:

Potassium: Lowest: ☐.☐ Highest: ☐.☐ mEq/L Single ☐ None ☐
Bicarbonate: Lowest: ☐☐.☐ Highest: ☐☐.☐ mEq/dL Single ☐ None ☐
BUN: Lowest: ☐☐.☐ Highest: ☐☐.☐ mg/dL Single ☐ None ☐
Creatinine: Lowest: ☐☐.☐☐ Highest: ☐☐.☐☐ mg/dL Single ☐ None ☐
Glucose: Lowest: ☐☐☐ Highest: ☐☐☐ mg/dL Single ☐ None ☐
Magnesium: Lowest: ☐.☐ Highest: ☐.☐ mmol/L Single ☐ None ☐
Phosphate Lowest: ☐.☐ Highest: ☐.☐ mg/dL Single ☐ None ☐
Albumin: Lowest: ☐.☐ Highest: ☐.☐ g/dL Single ☐ None ☐
Bilirubin: Lowest: ☐☐.☐ Highest: ☐☐.☐ mg/dL Single ☐ None ☐
Highest AST: ☐☐☐☐ U/L None ☐ Highest ALT: ☐☐☐☐ U/L None ☐

[25]**Highest/Lowest finger stick glucose every 6 hrs for last 24 hrs (if only single value, enter in**

Time Period	Lowest Glucose (mg/dL)	Date	Time	Highest Glucose	Date	Time	Single value	None
0601-1200								
1201-1800								
1801-2400								
0001-600								

"Lowest" field and check "Single value" box; If no data, check "None" box:

If patient was extubated/UAB >24 hours ago, go to question 34

[26]**Ventilator mode/parameters used in last 24 hrs** (check all that apply, circle the current one)

☐ **DRAEGER**

☐PC-CMV ☐VC-CMV ☐SPN-CPAP/PS
☐PC-AC ☐VC-AC ☐SPN-CPAP/VS
☐PC-SIMV ☐VC-SIMV ☐SPN-PPS
☐PC-BIPAP ☐VC-MMV ☐SPN-CPAP
☐PC-APRV
☐PC-HFO
☐PC-MMV
☐Other _____

☐**SERVO**

☐VC-AC ☐BiVent
☐PC-AC ☐PS
☐PRVC ☐VS
☐VC-SIMV ☐CPAP
☐PC-SIMV ☐NIV
☐PRVC-SIMV

[27]**Extubated:** ☐ Yes ☐ No If Yes, Date/Time of extubation: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

ARDSNet Ventilation Adherence Data (if still intubated and mechanically ventilated):

[28]Measured Tidal Volumes: Lowest: ☐☐☐☐ ml Highest: ☐☐☐☐ ml

[29]Estimated hours patient ventilated with tidal volume **> 7 ml/kg** ☐☐.☐ hrs

[30]Applied PEEP: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

[31]Mean airway pressure: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

Lung Physiology Parameters (recorded 0600 to 1000 day 2 post-randomization; If no data available, check "No values" box. If patient not intubated, check "Not intubated" box)

[32]Plateau Pressure: cm H_2O and associated PEEP: ☐☐ cm H_2O.

No values: ☐ Not intubated: ☐

Arterial Blood Gas (if only one value, record in "Lowest" field and check "Single value" box. If no ABG data check "None" box)

[33]PaO_2 /FiO_2: Lowest: ☐☐☐ mm Hg/☐☐☐ %Highest: ☐☐☐ mm Hg/☐☐☐ %mm Hg

Single Value: ☐ None: ☐

Fluid Management:

[34]Total Intake since randomization: ☐☐☐☐☐ mL

[35]Total Output since randomization (include dialysis/CRRT): ☐☐☐☐☐ mL

[36]**Plasma sample collected:** ☐ Yes ☐No

[37]Blood collected: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400) Processed: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[38]Number 0.5 ml aliquots: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

[39]Date/Time placed in -80°C freezer: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[40]Location in freezer: _____ Temperature reading on freezer: _____°C

DAILY DATA – Day 04

(to be obtained as close to 0800 as possible on day 2 after randomization)

[1]Form Completed by _____ MONTH / D D / Y Y Y Y TIME (0-2400)

[2]Vital status ☐ Alive ☐ Dead

[3]If Dead Date/Time of death: MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Cause of death (from discharge summary/discussion with ICU team), then skip to question 11.

☐ Respiratory failure ☐ Cardiac (arrhythmia, ACS, cardiogenic shock) ☐ Multi-organ failure

☐ Refractory shock ☐ Intraabdominal (perforation, compartment) ☐ Withdrawal of care

☐ Neurological devastation ☐ Severe sepsis ☐ Refractory acidosis ☐ Hemorrhage

[5]Still receiving NMB? ☐ Yes ☐ No

If No and discontinued in last 24 hrs, answer following questions:

[6]Date/Time discontinued: MONTH / D D / Y Y Y Y TIME (0-2400)

[7]Reason for discontinuation: ☐ Refractory bradycardia ☐ Possible drug reaction

☐ Decision of ICU provider ☐ Decision of family. ☐ As per Study protocol

[8]Date/Time: neuromuscular function (4 twitches/TOF) returned: MONTH / D D / Y Y Y Y TIME (0-2400)

or ☐Did not return

[9]Is patient in hypothermia group? ☐ Yes ☐ No **If "No" skip to question 13**

[10]Did patient complete 48 hours of cooling? ☐ Yes ☐ No **If "Yes" skip to question 14**

[11]If No, when was cooling stopped? MONTH / D D / Y Y Y Y TIME (0-2400)

[12]Reason for discontinuation: ☐ Refractory bradycardia with hypotension ☐ Hemorrhage

☐ Intractable ventricular arrhythmia ☐ Decision of ICU provider ☐ Decision of family

Skip to question 14.

[13]If in the Control arm, received therapeutic hypothermia in last 24 hrs? ☐ Yes ☐ No ☐ N/A

[14]Still intubated or receiving Assisted Breathing? ☐ Yes ☐ No ☐ N/A

If No, when was patient extubated or UAB for ≥48 hours? MONTH / D D / Y Y Y Y TIME (0-2400)

[15]Was RRT started in last 24 hrs? ☐ Yes ☐ No ☐ N/A

[16]If RRT had been previously initiated has it stopped since randomization? ☐Yes ☐No ☐N/A

[17]In the last 24 hrs did the patient have any of the following:

Bradycardia (with mean arterial pressure < 65 mm Hg or needing pressors) ☐ Yes ☐ No

Significant Bleeding (Required IR, Surgery or >3u pRBCs) ☐Yes ☐No

Diagnosis of new pneumonia ☐ Yes ☐ No

[18]**Vital signs in last 24 hrs**

Systolic BP: Lowest: ☐☐☐ Highest: ☐☐☐ mm Hg Single ☐

Diastolic BP: Lowest: ☐☐☐ Highest: ☐☐☐ mm Hg Single ☐

CVP: Lowest: ☐☐ Highest: ☐☐ cm H_2O CVP not available ☐ Single ☐

Mean arterial pressure: Lowest: ☐☐☐ Highest: ☐☐☐ mm Hg Single ☐

[19]For each 2 hr block for the last 24 hrs record highest and lowest temperature and lowest SpO_2 and the FiO_2 and Mean Airway Pressure measured closest to the SpO_2 reading. If only single temperature measurement for block, check "Single value" box. If no SpO_2 measured for block, check the "None" box.

Time period	Temp (°C) If only one value record as "Low" and check box	Site of Temp measurement	Low SpO_2 (%)*	FiO2 (%)	Mean airway pressure (cm H_2O)
0801 to 1000	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1001 to 1200	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1201 to 1400	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1401 to 1600	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1601 to 1800	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
1801 to 2000	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
2001 to 2200	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
2201 to 2400	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0001 to 0200	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0201 to 0400	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0401 to 0600	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			
0601- to 0800	High:	☐ Esophageal ☐ Urinary	None ☐		
	Low: ☐	☐ Peripheral ☐ IV			

In last 24 hours did patient receive?

[20]**Corticosteroid**: ☐Yes ☐No If yes, total daily dose (prednisone equivalent): ☐☐☐ mg

1 mg prednisone/methylprednisolone = 4 mg hydrocortisone; 1 mg dexamethasone = 25 mg hydrocortisone

[21]**Inhaled vasodilator:** ☐Yes ☐No If "Yes": indicate agent(s) used and total hrs administered

☐Epoprostenol ☐Nitric Oxide Total hours administered: ☐☐

[22]**Vasopressor support in last 24 hrs** ☐Yes ☐No **If No proceed to question 23**.
(check all received and highest infusion rate for each):

☐ Dobutamine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Dopamine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Norepinephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Epinephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Vasopressin ☐☐.☐☐ units/min
☐ Phenylephrine ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min
☐ Milrinone ☐☐.☐☐ ☐μg/kg/min OR ☐μg/min

Total hours receiving vasopressor support: ☐☐

[23]Did the patient start proning ☐Yes ☐No or stop proning ☐Yes ☐No in the last 24 hours?

[24] **Laboratory data (if only one value, record in "Lowest" field and click "Single" box; if no data, click "None" box):**

CBC values:

WBC: Lowest: ☐☐☐ Highest: ☐☐☐ x1000/mm^3 Single ☐ None ☐
Hgb: Lowest: ☐☐☐ Highest: ☐☐☐ g/dL Single ☐ None ☐
Hct: Lowest: ☐☐☐ Highest: ☐☐☐ % Single ☐ None ☐
Platelets: Lowest: ☐☐☐ x1000/mm^3 None ☐

Serum Levels:

Potassium: Lowest: ☐.☐ Highest: ☐.☐ mEq/L Single ☐ None ☐
Bicarbonate: Lowest: ☐☐.☐ Highest: ☐☐.☐ mEq/dL Single ☐ None ☐
BUN: Lowest: ☐☐.☐ Highest: ☐☐.☐ mg/dL Single ☐ None ☐
Creatinine: Lowest: ☐☐.☐☐ Highest: ☐☐.☐☐ mg/dL Single ☐ None ☐
Glucose: Lowest: ☐☐☐ Highest: ☐☐☐ mg/dL Single ☐ None ☐
Magnesium: Lowest: ☐.☐ Highest: ☐.☐ mmol/L Single ☐ None ☐
Phosphate Lowest: ☐.☐ Highest: ☐.☐ mg/dL Single ☐ None ☐
Albumin: Lowest: ☐.☐ Highest: ☐.☐ g/dL Single ☐ None ☐
Bilirubin: Lowest: ☐☐.☐ Highest: ☐☐.☐ mg/dL Single ☐ None ☐
Highest AST: ☐☐☐☐ U/L None ☐ Highest ALT: ☐☐☐☐ U/L None ☐

[25]**Highest/Lowest finger stick glucose every 6 hrs for last 24 hrs (if only single value, enter in**

Time Period	Lowest Glucose (mg/dL)	Date	Time	Highest Glucose	Date	Time	Single value	None
0601-1200								
1201-1800								
1801-2400								
0001-600								

"Lowest" field and check "Single value" box; If no data, check "None" box:

If patient was extubated/UAB >24 hours ago, go to question 34

[26]**Ventilator mode/parameters used in last 24 hrs** (check all that apply, circle the current one)

☐ **DRAEGER**

☐PC-CMV ☐VC-CMV ☐SPN-CPAP/PS
☐PC-AC ☐VC-AC ☐SPN-CPAP/VS
☐PC-SIMV ☐VC-SIMV ☐SPN-PPS
☐PC-BIPAP ☐VC-MMV ☐SPN-CPAP
☐PC-APRV
☐PC-HFO
☐PC-MMV
☐Other _____

☐**SERVO**

☐VC-AC ☐BiVent
☐PC-AC ☐PS
☐PRVC ☐VS
☐VC-SIMV ☐CPAP
☐PC-SIMV ☐NIV
☐PRVC-SIMV

[27]**Extubated:** ☐ Yes ☐ No If Yes, Date/Time of extubation: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

ARDSNet Ventilation Adherence Data (if still intubated and mechanically ventilated):

[28]Measured Tidal Volumes: Lowest: ☐☐☐☐ ml Highest: ☐☐☐☐ ml

[29]Estimated hours patient ventilated with tidal volume **> 7 ml/kg** ☐☐.☐ hrs

[30]Applied PEEP: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

[31]Mean airway pressure: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

Lung Physiology Parameters (recorded 0600 to 1000 day 2 post-randomization; If no data available, check "No values" box. If patient not intubated, check "Not intubated" box)

[32]Plateau Pressure: cm H_2O and associated PEEP: ☐☐ cm H_2O.

No values: ☐ Not intubated: ☐

Arterial Blood Gas (if only one value, record in "Lowest" field and check "Single value" box. If no ABG data check "None" box)

[33]PaO_2 /FiO_2: Lowest: ☐☐☐ mm Hg/☐☐☐ %Highest: ☐☐☐ mm Hg/☐☐☐ %mm Hg

Single Value: ☐ None: ☐

Fluid Management:

[34]Total Intake since randomization: ☐☐☐☐☐ mL

[35]Total Output since randomization (include dialysis/CRRT): ☐☐☐☐☐ mL

[36]**Plasma sample collected:** ☐ Yes ☐No

[37]Blood collected: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400) Processed: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[38]Number 0.5 ml aliquots: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

[39]Date/Time placed in -80°C freezer: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[40]Location in freezer: _____ Temperature reading on freezer: _____°C

DAILY DATA – Day 07

(to be obtained as close to 0800 as possible day 7 after randomization)

[1]Form Completed by _____ MONTH / D D / Y Y TIME (0-

[2]Vital status ☐ Alive ☐ Dead

[3]If Dead Date/Time of death: MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Cause of death (from discharge summary/discussion with ICU team), then skip to question 11.

☐ Respiratory failure ☐ Cardiac (arrhythmia, ACS, cardiogenic shock) ☐ Multi-organ failure

☐ Refractory shock ☐ Intraabdominal (perforation, compartment) ☐ Withdrawal of care

☐ Neurological devastation ☐ Severe sepsis ☐ Refractory acidosis ☐ Hemorrhage

[5]Still receiving NMB? ☐ Yes ☐ No

If No and discontinued in last 24 hrs, answer following questions:

[6]Date/Time discontinued: MONTH / D D / Y Y Y Y TIME (0-2400)

[7]Reason for discontinuation: ☐ Refractory bradycardia ☐ Possible drug reaction

☐ Decision of ICU provider ☐ Decision of family

[8]Date/Time: neuromuscular function (4 twitches/TOF) returned: MONTH / D D / Y Y Y Y TIME (0-2400)

or ☐Did not return

[9]Did the patient receive therapeutic hypothermia in last 72 hrs? ☐ Yes ☐ No

If "Yes" how for many hours ☐☐ and to what temperature (lowest)? ☐☐.☐ °C

[10]Still intubated or receiving Assisted Breathing? ☐ Yes ☐ No ☐ N/A

If No, when was patient extubated? MONTH / D D / Y Y Y TIME (0-2400)

[11]Was RRT started in last 24 hrs? ☐ Yes ☐ No ☐ N/A

[12]If RRT had been previously initiated has it stopped since randomization? ☐Yes ☐No ☐N/A

[13]In the last 24 hrs did the patient have any of the following:

Bradycardia (with mean arterial pressure < 65 mm Hg or needing pressors) ☐ Yes ☐ No

Significant Bleeding (Required IR, Surgery or >3u pRBCs) ☐Yes ☐No

Diagnosis of new pneumonia ☐ Yes ☐ No

[14]**Vital signs in last 24 hrs**

Systolic BP: Lowest: ☐☐☐ Highest: ☐☐☐ mm Hg Single ☐

Diastolic BP: Lowest: ☐☐☐ Highest: ☐☐☐ mm Hg Single ☐

CVP: Lowest: ☐☐ Highest: ☐☐ cm H_2O CVP not available ☐ Single ☐

Mean arterial pressure: Lowest: ☐☐☐ Highest: ☐☐☐ mm Hg Single ☐

[15]**For each 6 hr block for the last 72 hrs record the lowest SpO_2 and the FiO_2 and Mean Airway Pressure measured closest to the SpO_2 reading. If no SpO_2 measured for block, check the "None" box.**

Time Period	Date	Time	SpO_2 (pulse Ox) (%)	FiO2 (%)	Mean airway pressure (cm H_2O)
Day 4 after Randomization					
0600-1200					
1200-1800					
1800-2400					
Day 5 after Randomization					
00-600					
0600-1200					
1200-1800					
1800-2400					
Day 6 after Randomization					
00-600					
0600-1200					
1200-1800					
1800-2400					
Day 7 after Randomization					
00-600					

In last 24 hours did patient receive?

[16]**Corticosteroid**: ☐Yes ☐No If yes, total daily dose (prednisone equivalent): ☐☐☐ mg

1 mg prednisone/methylprednisolone = 4 mg hydrocortisone; 1 mg dexamethasone = 25 mg hydrocortisone

[17]**Inhaled vasodilator:** ☐Yes ☐No If "Yes": indicate agent(s) used and total hrs administered

☐Epoprostenol ☐Nitric Oxide Total hours administered: ☐☐

[18]**Vasopressor support in last 24 hrs** ☐Yes ☐No **If No proceed to question 19**.
(check all received and highest infusion rate for each):

☐ Dobutamine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
☐ Dopamine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
☐ Norepinephrine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
☐ Epinephrine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
☐ Vasopressin ☐☐.☐☐ units/min
☐ Phenylephrine ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min
☐ Milrinone ☐☐.☐☐ ☐µg/kg/min OR ☐µg/min

Total hours receiving vasopressor support: ☐☐

[19]Did the patient start proning ☐Yes ☐No or stop proning ☐Yes ☐No in the last 72 hours?

[20] **Laboratory data (if only one value, record in "Lowest" field and click "Single" box; if no data, click "None" box):**

CBC values:

WBC: Lowest: ☐☐☐ Highest: ☐☐☐ x1000/mm^3 Single ☐ None ☐

Hgb: Lowest: ☐☐☐ Highest: ☐☐☐ g/dL Single ☐ None ☐

Hct: Lowest: ☐☐☐ Highest: ☐☐☐ % Single ☐ None ☐

Platelets: Lowest: ☐☐☐ x1000/mm^3 None ☐

Serum Levels:

Potassium: Lowest: ☐.☐ Highest: ☐.☐ mEq/L Single ☐ None ☐

Bicarbonate: Lowest: ☐☐.☐ Highest: ☐☐.☐ mEq/dL Single ☐ None ☐

BUN: Lowest: ☐☐.☐ Highest: ☐☐.☐ mg/dL Single ☐ None ☐

Creatinine: Lowest: ☐☐.☐☐ Highest: ☐☐.☐☐ mg/dL Single ☐ None ☐

Glucose: Lowest: ☐☐☐ Highest: ☐☐☐ mg/dL Single ☐ None ☐

Magnesium: Lowest: ☐.☐ Highest: ☐.☐ mmol/L Single ☐ None ☐

Phosphate Lowest: ☐.☐ Highest: ☐.☐ mg/dL Single ☐ None ☐

Albumin: Lowest: ☐.☐ Highest: ☐.☐ g/dL Single ☐ None ☐

Bilirubin: Lowest: ☐☐.☐ Highest: ☐☐.☐ mg/dL Single ☐ None ☐

Highest AST: ☐☐☐☐ U/L None ☐ Highest ALT: ☐☐☐☐ U/L None ☐

If patient was extubated/UAB >24 hours ago, go to question 29.

[21] **Ventilator mode/parameters used in last 24 hrs** (check all that apply, circle the current one)

☐ **DRAEGER**

☐PC-CMV ☐VC-CMV ☐SPN-CPAP/PS

☐PC-AC ☐VC-AC ☐SPN-CPAP/VS

☐PC-SIMV ☐VC-SIMV ☐SPN-PPS

☐PC-BIPAP ☐VC-MMV ☐SPN-CPAP

☐PC-APRV

☐PC-HFO

☐PC-MMV

☐Other _____

☐**SERVO**

☐VC-AC ☐BiVent

☐PC-AC ☐PS

☐PRVC ☐VS

☐VC-SIMV ☐CPAP

☐PC-SIMV ☐NIV

☐PRVC-SIMV

[22] **Extubated:** ☐ Yes ☐ No If Yes, Date/Time of extubation: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐

MONTH D D Y Y Y Y TIME (0-2400)

ARDSNet Ventilation Adherence Data (if still intubated and mechanically ventilated):

[23] Measured Tidal Volumes: Lowest: ☐☐☐☐ ml Highest: ☐☐☐☐ ml

[24] Estimated hours patient ventilated with tidal volume **> 7 ml/kg** ☐☐.☐ hrs

[25] Applied PEEP: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

[26] Mean airway pressure: Lowest: ☐☐ cm H_2O Highest: ☐☐ cm H_2O

Lung Physiology Parameters (recorded 0600 to 1000 day 2 post-randomization; If no data available, check "No values" box. If patient not intubated, check "Not intubated" box)

[27]Plateau Pressure: cm H_2O and associated PEEP: cm H_2O.

No values: ☐ Not intubated: ☐

Arterial Blood Gas (if only one value, record in "Lowest" field and check "Single value" box. If no ABG data check "None" box)

[28]PaO_2 /FiO_2: Lowest: ☐☐☐ mm Hg/☐☐☐ % Highest: ☐☐☐ mm Hg/☐☐☐ % mm Hg

Single Value: ☐ None: ☐

Fluid Management:

[29]Total Intake since randomization: ☐☐☐☐☐ mL

[30]Total Output since randomization (include dialysis/CRRT): ☐☐☐☐☐ mL

[31]**Plasma sample collected:** ☐ Yes ☐No

[32]Blood collected: ☐☐☐/☐☐/☐☐☐☐ (MONTH D D Y Y Y Y) ☐☐☐☐ (TIME (0-2400)) Processed: ☐☐☐/☐☐/☐☐☐☐ (MONTH D D Y Y Y Y) ☐☐☐☐ (TIME (0-2400))

[33]Number 0.5 ml aliquots: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

[34]Date/Time placed in -80°C freezer: ☐☐☐/☐☐/☐☐☐☐ (MONTH D D Y Y Y Y) ☐☐☐☐ (TIME (0-2400))

[35]Location in freezer: _____ Temperature reading on freezer: _____°C

Unassisted Breathing Checklist (for Study Day 1-28)

A period of unassisted breathing is defined as ≥48 continuous UAB, which includes:

1./ spontaneously breathing with face mask, nasal prong oxygen including high flow, or room air
2./ T-tube breathing
3./ tracheostomy mask breathing
4./ CPAP ≤5 cm H2O without PS or IMV assistance
5./ use of CPAP or BIPAP solely for sleep apnea management

Fill out one section for each continuous period of UAB lasting ≥48 hrs up through study day 28.

A ventilator-free day is defined as a day (0800 to 0800) without any assisted breathing except for assisted breathing administered for <24 hrs solely for a surgical or other procedure.

Transition to Unassisted Breathing Checklist #1:

[1]Data entered by _____ Date/Time UAB started: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[2]Spontaneous Breathing Trial performed? ☐Yes ☐No

[3]Mode used for SBT: ☐PSV ___ / ___ cm H_2O ☐CPAP ___ cm H_2O ☐T-piece ☐trach collar

[4]Duration of SBT prior to removal of mechanical ventilation: ☐☐.☐ hours

[5]Regarding SBT:

1. Was $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mm Hg? ☐ Yes ☐No
2. Was Mean spontaneous tidal volume ≥ 4 ml/kg PBW? ☐Yes ☐No ☐Not measured
3. Was Respiratory Rate ≤ 35/min? ☐ Yes ☐ No
4. What was Rapid shallow breathing index? (RR/TV) ☐☐☐
5. Was pH ≥ 7.30 on VBG or ABG ☐Yes ☐No ☐Not measured
6. Did the patient have respiratory distress (2 or more of the following)? ☐ Yes ☐No
   a. Heart rate ≥ 120% of the 0600 rate for >5 min)
   b. Marked use of accessory muscles
   c. Abdominal paradox
   d. Diaphoresis
   e. Marked subjective dyspnea

[6]Continuous unassisted breathing through study day 28: ☐ Yes ☐No

[7]If No, Date/Time ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ and reason for re-initiation of ventilation
MONTH D D Y Y Y Y TIME (0-2400)

_____.

[8]Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ☐☐

[9]Data entry completed by _____ Date/Time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

Transition to Unassisted Breathing Checklist #2:

[1]Data entered by _____ Date/Time: MONTH D D / Y Y Y Y / TIME (0-2400)

[2]Spontaneous Breathing Trial performed? ☐Yes ☐No

[3]Mode used for SBT: ☐PSV ___ / ___ cm H_2O ☐CPAP___ cm H_2O ☐T-piece ☐trach collar

[4]Duration of SBT prior to removal of mechanical ventilation: ☐☐.☐ hours

[5] Regarding SBT:

1. Was $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mm Hg? ☐ Yes ☐No
2. Was Mean spontaneous tidal volume ≥ 4 ml/kg PBW? ☐Yes ☐No ☐Not measured
3. Was Respiratory Rate ≤ 35/min? ☐ Yes ☐ No
4. What was Rapid shallow breathing index? (RR/TV) ☐☐☐
5. Was pH ≥ 7.30 on VBG or ABG ☐Yes ☐No ☐Not measured
6. Did the patient have respiratory distress (2 or more of the following)? ☐ Yes ☐No

No respiratory distress (defined as 2 or more of the following): ☐ Yes ☐No

a. Heart rate ≥ 120% of the 0600 rate for >5 min)
b. Marked use of accessory muscles
c. Abdominal paradox
d. Diaphoresis
e. Marked subjective dyspnea

[6]Continuous unassisted breathing through study day 28: ☐ Yes ☐No

[7]If No, Date/Time MONTH D D / Y Y Y Y / TIME (0-2400) and reason for re-initiation of ventilation

_____.

[8]Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ☐☐

[9]Data entry completed by _____ Date/Time: MONTH D D / Y Y Y Y / TIME (0-2400)

Transition to Unassisted Breathing Checklist #3:

[1]Data entered by _____ Date/Time: MONTH D D / Y Y Y Y / TIME (0-2400)

[2]Spontaneous Breathing Trial performed? ☐Yes ☐No

[3]Mode used for SBT: ☐PSV ___ / ___ cm H_2O ☐CPAP ___ cm H_2O ☐T-piece ☐trach collar

[4]Duration of SBT prior to removal of mechanical ventilation: ☐☐.☐ hours

[5] Regarding SBT:

1. Was $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mm Hg? ☐ Yes ☐No
2. Was Mean spontaneous tidal volume ≥ 4 ml/kg PBW? ☐Yes ☐No ☐Not measured
3. Was Respiratory Rate ≤ 35/min? ☐ Yes ☐ No
4. What was Rapid shallow breathing index? (RR/TV) ☐☐☐
5. Was pH ≥ 7.30 on VBG or ABG ☐Yes ☐No ☐Not measured
6. Did the patient have respiratory distress (2 or more of the following)? ☐ Yes ☐No
   a. Heart rate ≥ 120% of the 0600 rate for >5 min)
   b. Marked use of accessory muscles
   c. Abdominal paradox
   d. Diaphoresis
   e. Marked subjective dyspnea

[6]Continuous unassisted breathing through study day 28: ☐ Yes ☐No

[7]If No, Date/Time MONTH D D / Y Y Y Y / TIME (0-2400) and reason for re-initiation of ventilation

_____.

[8]Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ☐☐

[9]Data entry completed by _____ Date/Time: MONTH D D / Y Y Y Y / TIME (0-2400)

Transition to Unassisted Breathing Checklist #4:

[1]Data entered by _____ Date/Time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

[2]Spontaneous Breathing Trial performed? ☐Yes ☐No

[3]Mode used for SBT: ☐PSV ___ / ___ cm H_2O ☐CPAP___ cm H_2O ☐T-piece ☐trach collar

[4]Duration of SBT prior to removal of mechanical ventilation: ☐☐.☐ hours

[5] Regarding SBT:

1. Was $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mm Hg? ☐ Yes ☐No
2. Was Mean spontaneous tidal volume ≥ 4 ml/kg PBW? ☐Yes ☐No ☐Not measured
3. Was Respiratory Rate ≤ 35/min? ☐ Yes ☐ No
4. What was Rapid shallow breathing index? (RR/TV) ☐☐☐
5. Was pH ≥ 7.30 on VBG or ABG ☐Yes ☐No ☐Not measured
6. Did the patient have respiratory distress (2 or more of the following)? ☐ Yes ☐No
   a. Heart rate ≥ 120% of the 0600 rate for >5 min)
   b. Marked use of accessory muscles
   c. Abdominal paradox
   d. Diaphoresis
   e. Marked subjective dyspnea

[6]Continuous unassisted breathing through study day 28: ☐ Yes ☐No

[7]If No, Date/Time ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ and reason for re-initiation of ventilation
MONTH D D Y Y Y Y TIME (0-2400)

_____.

[8]Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ☐☐

[9]Data entry completed by _____ Date/Time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐
MONTH D D Y Y Y Y TIME (0-2400)

Transition to Unassisted Breathing Checklist #5:

[1]Data entered by _____ Date/Time: MONTH D D / Y Y Y Y / TIME (0-2400)

[2]Spontaneous Breathing Trial performed? ☐Yes ☐No

[3]Mode used for SBT: ☐PSV ___ / ___ cm H_2O ☐CPAP___ cm H_2O ☐T-piece ☐trach collar

[4]Duration of SBT prior to removal of mechanical ventilation: ☐☐.☐ hours

5 Regarding SBT:

1. Was $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mm Hg? ☐ Yes ☐No
2. Was Mean spontaneous tidal volume ≥ 4 ml/kg PBW? ☐Yes ☐No ☐Not measured
3. Was Respiratory Rate ≤ 35/min? ☐ Yes ☐ No
4. What was Rapid shallow breathing index? (RR/TV)
5. Was pH ≥ 7.30 on VBG or ABG ☐Yes ☐No ☐Not measured
6. Did the patient have respiratory distress (2 or more of the following)? ☐ Yes ☐No
   a. Heart rate ≥ 120% of the 0600 rate for >5 min)
   b. Marked use of accessory muscles
   c. Abdominal paradox
   d. Diaphoresis
   e. Marked subjective dyspnea

[6]Continuous unassisted breathing through study day 28: ☐ Yes ☐No

[7]If No, Date/Time MONTH D D / Y Y Y Y / TIME (0-2400) and reason for re-initiation of ventilation

_____.

[8]Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ☐☐

[9]Data entry completed by _____ Date/Time: MONTH D D / Y Y Y Y / TIME (0-2400)

SITE ID | PATIENT ID | LETTER CODE

Initial ICU Discharge Checklist

An ICU-free period is defined as ≥ 48 continuous hours with active transfer/discharge from ICU order or in non-ICU setting.

Fill out one section for each continuous period of UAB lasting ≥48 hrs up through study day 28.

An ICU-free day is defined as a day (0800 to 0800) in which the patient is ICU-free.

[1]Form completed by _____ MONTH / D D / Y Y Y Y TIME (0-2400)

[2]Date/time (0-2400) of ICU discharge/transfer order: MONTH / D D / Y Y Y Y TIME (0-2400)

[3]Date/time of ICU discharge/transfer? MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Disposition:

- ☐ Died
- ☐ Acute care floor
- ☐ Acute care floor of another hospital
- ☐ ICU in another hospital
- ☐ Home
- ☐ Acute Rehabilitation facility
- ☐ Subacute Rehabilitation facility
- ☐ LTAC
- ☐ Skilled nursing facility

[5]Was the patient still receiving Assisted Breathing at time of transfer/discharge? ☐ Yes ☐ No

If no, date last on ventilator: MONTH / D D / Y Y Y Y

[6]Was the patient using supplemental oxygen at time of transfer/discharge? ☐ Yes ☐ No

If Yes, indicate route and level:

☐ High Flow Nasal cannula: ☐☐ LPM and ☐☐☐ % oxygen

☐ Nasal cannula: ☐☐ LPM

☐ Trach collar: ☐☐☐ % oxygen

☐ Face mask: ☐☐☐ % oxygen

[7]Result of MOCA: /30 points ☐☐

[8]Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28?

☐ Yes ☐ No

[9]If Yes, Date/Time of cancellation/readmission MONTH / D D / Y Y Y Y TIME (0-2400)

[10]Number of ICU-free days from this ICU-free period (days 0800 to 0800 with an active transfer/discharge order or in non-ICU setting): ☐☐

[11]Data entry completed by _____ Date/Time: MONTH / D D / Y Y Y Y TIME (0-2400)

Subsequent ICU Discharge #1 Checklist

(fill out one form for each ICU discharge within the first 28 days)

[1]Form completed by _____ MONTH / D D / Y Y Y Y TIME (0-2400)

[2]Date/time (0-2400) of ICU discharge/transfer order: MONTH / D D / Y Y Y Y TIME (0-2400)

[3]Date/time of ICU discharge/transfer? MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Disposition:

- ☐ Died
- ☐ Acute care floor
- ☐ Acute care floor of another hospital
- ☐ ICU in another hospital
- ☐ Home
- ☐ Acute Rehabilitation facility
- ☐ Subacute Rehabilitation facility
- ☐ LTAC
- ☐ Skilled nursing facility

[5]Was the patient still receiving Assisted Breathing at time of transfer/discharge? ☐ Yes ☐ No

If no, date last on ventilator: MONTH / D D / Y Y Y Y

[6]Was the patient using supplemental oxygen at time of transfer/discharge? ☐ Yes ☐ No

If Yes, indicate route and level:

☐ High Flow Nasal cannula: ☐☐ LPM and ☐☐☐ % oxygen

☐ Nasal cannula: ☐☐ LPM

☐ Trach collar: ☐☐☐ % oxygen

☐ Face mask: ☐☐☐ % oxygen

[7]Result of MOCA: /30 points ☐☐

[8]Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28?

☐ Yes ☐ No

[9]If Yes, Date/Time of cancellation/readmission MONTH / D D / Y Y Y Y TIME (0-2400)

[10]Number of ICU-free days from this ICU-free period (days 0800 to 0800 with an active transfer/discharge order or in non-ICU setting): ☐☐

[11]Data entry completed by _____ Date/Time: MONTH / D D / Y Y Y Y TIME (0-2400)

Subsequent ICU Discharge #2 Checklist

(fill out one form for each ICU discharge within the first 28 days)

[1]Form completed by _____ MONTH / D D / Y Y Y Y TIME (0-2400)

[2]Date/time (0-2400) of ICU discharge/transfer order: MONTH / D D / Y Y Y Y TIME (0-2400)

[3]Date/time of ICU discharge/transfer? MONTH / D D / Y Y Y Y TIME (0-2400)

[4]Disposition:

- ☐ Died
- ☐ Acute care floor
- ☐ Acute care floor of another hospital
- ☐ ICU in another hospital
- ☐ Home
- ☐ Acute Rehabilitation facility
- ☐ Subacute Rehabilitation facility
- ☐ LTAC
- ☐ Skilled nursing facility

[5]Was the patient still receiving Assisted Breathing at time of transfer/discharge? ☐ Yes ☐ No

If no, date last on ventilator: MONTH / D D / Y Y Y Y

[6]Was the patient using supplemental oxygen at time of transfer/discharge? ☐ Yes ☐ No

If Yes, indicate route and level:

☐ High Flow Nasal cannula: ☐☐ LPM and ☐☐☐ % oxygen

☐ Nasal cannula: ☐☐ LPM

☐ Trach collar: ☐☐☐ % oxygen

☐ Face mask: ☐☐☐ % oxygen

[7]Result of MOCA: /30 points ☐☐

[8]Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28?

☐ Yes ☐ No

[9]If Yes, Date/Time of cancellation/readmission MONTH / D D / Y Y Y Y TIME (0-2400)

[10]Number of ICU-free days from this ICU-free period (days 0800 to 0800 with an active transfer/discharge order or in non-ICU setting): ☐☐

[11]Data entry completed by _____ Date/Time: MONTH / D D / Y Y Y Y TIME (0-2400)

Subsequent ICU Discharge #3 Checklist

(fill out one form for each ICU discharge within the first 28 days)

[1]Form completed by _____

[2]Date/time (0-2400) of ICU discharge/transfer order: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[3]Date/time of ICU discharge/transfer? ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[4]Disposition:

- ☐ Died
- ☐ Acute care floor
- ☐ Acute care floor of another hospital
- ☐ ICU in another hospital
- ☐ Home
- ☐ Acute Rehabilitation facility
- ☐ Subacute Rehabilitation facility
- ☐ LTAC
- ☐ Skilled nursing facility

[5]Was the patient still receiving Assisted Breathing at time of transfer/discharge? ☐ Yes ☐ No

If no, date last on ventilator: ☐☐☐/☐☐/☐☐☐☐ MONTH D D Y Y Y Y

[6]Was the patient using supplemental oxygen at time of transfer/discharge? ☐ Yes ☐ No

If Yes, indicate route and level:

- ☐ High Flow Nasal cannula: ☐☐ LPM and ☐☐☐ % oxygen
- ☐ Nasal cannula: ☐☐ LPM
- ☐ Trach collar: ☐☐☐ % oxygen
- ☐ Face mask: ☐☐☐ % oxygen

[7]Result of MOCA: /30 points ☐☐

[8]Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28?
☐ Yes ☐ No

[9]If Yes, Date/Time of cancellation/readmission ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[10]Number of ICU-free days from this ICU-free period (days 0800 to 0800 with an active transfer/discharge order or in non-ICU setting): ☐☐

[11]Data entry completed by _____ Date/Time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

Subsequent ICU Discharge #4 Checklist

(fill out one form for each ICU discharge within the first 28 days)

[1]Form completed by _____

[2]Date/time (0-2400) of ICU discharge/transfer order: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[3]Date/time of ICU discharge/transfer? ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[4]Disposition:

- ☐ Died
- ☐ Acute care floor
- ☐ Acute care floor of another hospital
- ☐ ICU in another hospital
- ☐ Home
- ☐ Acute Rehabilitation facility
- ☐ Subacute Rehabilitation facility
- ☐ LTAC
- ☐ Skilled nursing facility

[5]Was the patient still receiving Assisted Breathing at time of transfer/discharge? ☐ Yes ☐ No

If no, date last on ventilator: ☐☐☐/☐☐/☐☐☐☐ MONTH D D Y Y Y Y

[6]Was the patient using supplemental oxygen at time of transfer/discharge? ☐ Yes ☐ No

If Yes, indicate route and level:

- ☐ High Flow Nasal cannula: ☐☐ LPM and ☐☐☐ % oxygen
- ☐ Nasal cannula: ☐☐ LPM
- ☐ Trach collar: ☐☐☐ % oxygen
- ☐ Face mask: ☐☐☐ % oxygen

[7]Result of MOCA: /30 points ☐☐

[8]Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28?
☐ Yes ☐ No

[9]If Yes, Date/Time of cancellation/readmission ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

[10]Number of ICU-free days from this ICU-free period (days 0800 to 0800 with an active transfer/discharge order or in non-ICU setting): ☐☐

[11]Data entry completed by _____ Date/Time: ☐☐☐/☐☐/☐☐☐☐ ☐☐☐☐ MONTH D D Y Y Y Y TIME (0-2400)

SITE ID PATIENT ID LETTER CODE

Day 28 Data Summary

[1]Form completed by: _____ ___/___/____ MONTH D D Y Y Y Y

[2]Vital status ☐ Alive ☐ Dead

[3] If Dead Date/Time of death: ___/___/____ ____ MONTH D D Y Y Y Y TIME (0-2400)

Cause of death (from discharge summary/discussion with ICU team):

☐ Respiratory failure ☐ Cardiac (arrhythmia, ACS, cardiogenic shock) ☐ Multi-organ failure
☐ Refractory shock ☐ Intraabdominal (perforation, compartment) ☐ Withdrawal of care
☐ Severe sepsis ☐ Neurological devastation ☐ Hemorrhage

[4]Has the patient received any mechanical ventilation in the past 48 hours? ☐ Yes ☐ No

If No, date last on ventilator: ___/___/____ MONTH D D Y Y Y Y

[5]Is the patient still in the ICU? ☐ Yes ☐ No

If no, date of transfer or discharge: ___/___/____ MONTH D D Y Y Y Y

Location of patient:
☐ Acute care floor
☐ Acute care floor in another hospital
☐ ICU in another hospital
☐ Home
☐ acute Rehabilitation facility
☐ Subacute Rehabilitation facility
☐ LTAC
☐ Skilled nursing facility

[6]**<u>Calculation of 28-day Ventilator-free days (VFDs)</u>:**

1. If patient is alive at 28 days, add ventilator-free days from all UAB periods from the UAB CRF. If the patient died before day 28, enter 0: ☐☐

[7]**<u>Calculation of 28-day ICU-free days (ICU-FDs)</u>:**

1. If patient is alive at 28 days, add ICU-free days from all ICU-free periods from the ICU Discharge CRF. If the patient died before day 28, enter 0: ☐☐

SITE ID PATIENT ID LETTER CODE

Hospital Discharge

[1]Form completed by: _____ MONTH / D D / Y Y Y Y

[2]Date of hospital discharge: MONTH / D D / Y Y Y Y

[3]Patient is being discharged from:
- ☐ acute care floor of hospital
- ☐ ICU

[4]Disposition:
- ☐ Dead
- ☐ Acute care floor
- ☐ Acute care floor of another hospital
- ☐ ICU in another hospital
- ☐ Home
- ☐ acute Rehabilitation facility
- ☐ Subacute Rehabilitation facility
- ☐ LTAC
- ☐ Skilled nursing facility

[5]Was the patient still receiving Assisted Breathing at hospital discharge? ☐ Yes ☐ No

[6]If no, date last received Assisted Breathing: MONTH / D D / Y Y Y Y

[7]Was the patient using supplemental oxygen at hospital discharge: ☐ Yes ☐ No

[8]If Yes, indicate route and level:
- ☐ High Flow Nasal cannula: ☐☐ LPM and ☐☐☐ % oxygen
- ☐ Nasal cannula: ☐☐ LPM
- ☐ Trach collar: ☐☐☐ % oxygen
- ☐ Face mask: ☐☐☐ % oxygen

[9]Result of MOCA: /30 points ☐☐

Enter Contact information (for 60- and 90-day follow-up):

Patient:
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Legally Authorized Representative (Name): _____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Additional Contact 1: Name:_____ Relationship to patient:_____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Additional Contact 2: Name:_____ Relationship to patient:_____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Additional Contact 3: Name:_____ Relationship to patient:_____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Additional Contact 4: Name:_____ Relationship to patient:_____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Additional Contact 5: Name:_____ Relationship to patient:_____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

Additional Contact 6: Name:_____ Relationship to patient:_____
Home Phone: ☐☐☐-☐☐☐-☐☐☐☐ Cell: ☐☐☐-☐☐☐-☐☐☐☐
Email:_____

SITE ID PATIENT ID LETTER CODE

COVID-CHILL Pilot Adverse Event Reporting (Ver. 1.0)

[1]Did the patient have any Adverse Events? ☐ Yes ☐ No

	AE #1	AE #2	AE #3
[2]Description			
[3]Reported by:			
[4]Date started	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?
[5]Time started	TIME (0-2400) ?	TIME (0-2400) ?	TIME (0-2400) ?
[6]Date resolved	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?
[7]Time resolved	TIME (0-2400) ?	TIME (0-2400) ?	TIME (0-2400) ?
[8]Severity (description-grade)	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 ☐ Life threatening – 4 ☐ Fatal - 5	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 ☐ Life threatening – 4 ☐ Fatal - 5	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 ☐ Life threatening – 4 ☐ Fatal - 5
[9]Serious?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
[10]Expected?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
[11]Relation to study intervention	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
[12]Action taken with study intervention	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped
[13]Other action taken	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____
[14]Outcome	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown
[15]Assessment made by (investigator name)			
[16]Date of Assessment	MONTH D D Y Y Y Y	MONTH D D Y Y Y Y	MONTH D D Y Y Y Y

SITE ID | PATIENT ID | LETTER CODE

	AE #4	AE #5	AE #6
[2]Description			
[3]Reported by:			
[4]Date started	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?
[5]Time started	TIME (0-2400) ?	TIME (0-2400) ?	TIME (0-2400) ?
[6]Date resolved	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?	MONTH D D Y Y Y Y ?
[7]Time resolved	TIME (0-2400) ?	TIME (0-2400) ?	TIME (0-2400) ?
[8]Severity (description-grade)	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 Life threatening – 4 ☐ Fatal - 5	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 Life threatening – 4 ☐ Fatal - 5	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 Life threatening – 4 ☐ Fatal - 5
[9]Serious?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
[10]Expected?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
[11]Relation to study intervention	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
[12]Action taken with study intervention	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped
[13]Other action taken	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____
[14]Outcome	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown
[15]Assessment made by (investigator name)			
[16]Date of Assessment	MONTH D D Y Y Y Y	MONTH D D Y Y Y Y	MONTH D D Y Y Y Y

SITE ID | PATIENT ID | LETTER CODE

	AE #7	AE #8	AE #9
[2]Description			
[3]Reported by:			
[4]Date started	☐☐☐/☐☐/☐☐☐☐ ☐ ? MONTH D D Y Y Y Y	☐☐☐/☐☐/☐☐☐☐ ☐ ? MONTH D D Y Y Y Y	☐☐☐/☐☐/☐☐☐☐ ☐ ? MONTH D D Y Y Y Y
[5]Time started	☐☐☐☐ ☐ ? TIME (0-2400)	☐☐☐☐ ☐ ? TIME (0-2400)	☐☐☐☐ ☐ ? TIME (0-2400)
[6]Date resolved	☐☐☐/☐☐/☐☐☐☐ ☐ ? MONTH D D Y Y Y Y	☐☐☐/☐☐/☐☐☐☐ ☐ ? MONTH D D Y Y Y Y	☐☐☐/☐☐/☐☐☐☐ ☐ ? MONTH D D Y Y Y Y
[7]Time resolved	☐☐☐☐ ☐ ? TIME (0-2400)	☐☐☐☐ ☐ ? TIME (0-2400)	☐☐☐☐ ☐ ? TIME (0-2400)
[8]Severity (description-grade)	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 ☐ Life threatening – 4 ☐ Fatal - 5	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 ☐ Life threatening – 4 ☐ Fatal - 5	☐ Mild - 1 ☐ Moderate - 2 ☐ Severe - 3 ☐ Life threatening – 4 ☐ Fatal - 5
[9]Serious?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
[10]Expected?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
[11]Relation to study intervention	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ Not related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
[12]Action taken with study intervention	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped	☐ Not changed ☐ Hypothermia stopped ☐ NMB stopped
[13]Other action taken	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____	☐ None ☐ Concomitant med ☐ Discontinue from study ☐ Other_____
[14]Outcome	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown	☐ Fatal ☐ Not recovered ☐ Not resolved ☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Unknown
[15]Assessment made by (investigator name)			
[16]Date of Assessment	☐☐☐/☐☐/☐☐☐☐ MONTH D D Y Y Y Y	☐☐☐/☐☐/☐☐☐☐ MONTH D D Y Y Y Y	☐☐☐/☐☐/☐☐☐☐ MONTH D D Y Y Y Y

SITE ID | PATIENT ID | LETTER CODE

60 Day-Telephone Contact

[1]☐ *Telephone contact with patient or LAR not completed (Complete the Subject Deviation form)*

	Date of Contact Attempt	Time (24hr)	Name of caller	Contact Occurred	Outcome if no contact
Contact Attempt #1	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____
Contact Attempt #2	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____
Contact Attempt #3	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____
Contact Attempt #4	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____

[2]Was information obtained directly from the study patient? ☐ Yes ☐ No

[3]If No, name of person who provided information: _____

[4]Relationwhip to subject: _____

[5]Was this individual the Legal Authorized Representative? ☐ Yes ☐ No

Telephone Contact *(continued)*

QUESTION(S) TO BE ASKED	
[6]Is the patient still alive?	☐ Yes ☐ No
[7]Ambulating without assistance?	☐ Yes ☐ No
[8]Need mechanical ventilation for any part of the day (other than treatment for obstructive sleep apnea)	☐ Yes ☐ No
[9]Need supplemental oxygen	☐ Yes ☐ No
[10]Location of patient	☐ Home ☐ Acute Care Hospital ☐ Rehab ☐ LTAC ☐ Supervised living

COMMENTS:

_____

_____

_____

_____

_____

_____

_____

_____

[11]**FORM COMPLETED BY:**_____ **DATE:** ☐☐☐/☐☐/☐☐☐☐

MONTH D D Y Y Y Y

SITE ID | PATIENT ID | LETTER CODE

90 Day-Telephone Contact

[1]☐ *Telephone contact with patient or LAR not completed (Complete the Subject Deviation form)*

	Date of Contact Attempt	Time (24hr)	Name of caller	Contact Occurred	Outcome if no contact
Contact Attempt #1	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____
Contact Attempt #2	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____
Contact Attempt #3	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____
Contact Attempt #4	MONTH D D / Y Y Y Y	TIME (0-2400)		☐[1] Yes ☐[0] No	☐[1] No answer ☐[2] Left Voice message ☐[3] Left Message w/_____ ☐[4] Line Busy ☐[5] Other: _____

[2]Was information obtained directly from the study patient? ☐ Yes ☐ No

[3]If No, name of person who provided information: _____

[4]Relationwhip to subject: _____

[5]Was this individual the Legal Authorized Representative? ☐ Yes ☐ No

Telephone Contact *(continued)*

QUESTION(S) TO BE ASKED	
[6]Is the patient still alive?	☐ Yes ☐ No
[7]Ambulating without assistance?	☐ Yes ☐ No
[8]Need mechanical ventilation for any part of the day (other than treatment for obstructive sleep apnea)	☐ Yes ☐ No
[9]Need supplemental oxygen	☐ Yes ☐ No
[10]Location of patient	☐ Home ☐ Acute Care Hospital ☐ Rehab ☐ LTAC ☐ Supervised living

COMMENTS:

[11]**FORM COMPLETED BY:**_____ **DATE:** __ __ / __ __ / __ __ __ __

MONTH D D Y Y Y Y

SITE ID | PATIENT ID | LETTER CODE

Summary of Patient Outcomes

[1]Form completed by: _____ MONTH / D D / Y Y Y Y TIME (0-2400)

[2]Date of discharge/death: MONTH / D D / Y Y Y Y

[3]Disposition

☐ Home without assisted breathing
☐ Home with assisted breathing
☐ Acute care hospital without assisted breathing
☐ Acute with assisted breathing
☐ NH/assisted living without assisted breathing
☐ NH/assisted living with assisted breathing
☐ Died prior to home without assisted breathing
☐ Died prior to home with assisted breathing

[4]Was this patient permanently withdrawn from the trial before day 28? ☐ Yes ☐ No

DATE: MONTH / D D / Y Y Y Y

Reason for withdrawal: ☐Death ☐ECMO ☐Other SAE ☐LAR choice ☐Provider choice

[5]Was patient discharged alive from the study hospital by day 90? ☐ Yes ☐ No

DISCHARGE DATE: MONTH / D D / Y Y Y Y

[6]If discharged prior to day 90 was the patient readmitted to an acute care hospital by study day 90?

☐Yes ☐No READMISSION DATE: MONTH / D D / Y Y Y Y

[7]If in the cooling group did the patient complete the cooling protocol ☐ Yes ☐ No ☐ N/A

If No, reason for early termination: _____

Total hours cooled: ___

[8]If in the control group did the patient receive hypothermia before day 28? ☐ Yes ☐ No

If Yes, study day cooling started ___ and ended ___

and the range of temperatures during the cooling period: __.__ to __.__ °C.

[9]Was the patient alive by study day 90? ☐ Yes ☐ No ☐ Unknown

If NO, Date of Death: MONTH / D D / Y Y Y Y

Cause of death (from discharge summary/discussion with ICU team):

☐ Respiratory failure
☐ Cardiac (arrhythmia, ACS, cardiogenic shock)
☐ Multi-organ failure
☐ Refractory shock
☐ Intraabdominal (perforation, compartment)
☐ Withdrawal of care
☐ Severe sepsis
☐ Neurological devastation
☐ Hemorrhage

[10]Unassisted breathing for ≥48 hours by day 28? ☐ Yes ☐ No
If Yes, enter first date UAB began: ☐☐☐/☐☐/☐☐☐☐
MONTH D D Y Y Y Y

[11]Was patient extubated by day 28? ☐ Yes ☐ No
If Yes, enter date of extubation: ☐☐☐/☐☐/☐☐☐☐
MONTH D D Y Y Y Y

[12]Did the subject undergo tracheostomy by day 28? ☐ Yes ☐ No
If Yes, enter date of tracheostomy: ☐☐☐/☐☐/☐☐☐☐
MONTH D D Y Y Y Y

[13]Was the patient discharged/transferred to a non-ICU setting by day 28? ☐ Yes ☐ No
If Yes, enter date of discharge/transfer: ☐☐☐/☐☐/☐☐☐☐
MONTH D D Y Y Y Y

[14]Was the patient receiving prone positioning at randomization? ☐ Yes ☐ No
If Yes, Study day when patient received final prone positioning: ☐☐

[15]If No, did patient receive proning during the first 28 study days: ☐ Yes ☐ No
If Yes, study day proning started ☐☐ and ended ☐☐

Ventilator days until UAB at home, death or day 90 is any day patient received assisted breathing except for <24hr related to procedure/surgery

Patient achieved UAB? ☐ No ☐ Yes Date of 1st UAB: MONTH D D Y Y Y Y

Patient returned to assisted breathing ☐ No ☐ Yes Date of return to AB: MONTH D D Y Y Y Y

Patient achieved UAB again? ☐ No ☐ Yes Date of 2nd UAB: MONTH D D Y Y Y Y

Patient returned to assisted breathing again ☐ No ☐ Yes Date of return to AB: MONTH D D Y Y Y Y

Patient achieved UAB again? ☐ No ☐ Yes Date of 3rd UAB: MONTH D D Y Y Y Y

Patient returned to assisted breathing again ☐ No ☐ Yes Date of return to AB: MONTH D D Y Y Y Y

Patient achieved UAB again? ☐ No ☐ Yes Date of 4th UAB MONTH D D Y Y Y Y

End of life decision making (for all pts alive and dead)
- ☐ No DNR decision made
- ☐ DNR decision made-withhold only CPR (CR or PR)
- ☐DNR decision made-withhold life support and CPR
- ☐DNR decision made-withdraw life support
- ☐Diagnosis of brain death
- ☐Unknown/can't tell

Was written consent obtained from the subject during hospitalization?
- ☐Yes
- ☐No, reason
  - ☐patient died
  - ☐Patient never regained decision-making capacity
  - ☐Patient declined further participation in study
  - ☐Other

Did patient require dialysis during Study hospitalization?
- ☐Yes If yes, enter dates of first and last dialysis:
  Date of first dialysis: _____ Date of last dialysis: _____
- ☐No