Study Title: Pilot Randomized Clinical Trial of Therapeutic Hypothermia vs. Standard of Care in Patients With Moderate to Severe ARDS Receiving Continuous Infusion of a Neuromuscular Blocking Agent - the Cooling to Help Injured Lungs (CHILL) Pilot Study

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CHILL-pilot:
Cooling to Help Injured Lungs
Pilot Study
(Self-funded Phase)

Manual of Operations

Version 1.4

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1 Study Overview

1.1 Study Synopsis

The Cooling to Help Injured Lungs (CHILL) program is intended to test the safety and benefit of therapeutic hypothermia (TH) in patients with ARDS. The hypothesis that TH will reduce lung injury in ARDS is based on two decades of basic research, retrospective clinical data, an older small non-randomized trial, and our recent small open-label pilot trial. To avoid the major complication of cooling, shivering and its metabolic consequences, we will initially test the effectiveness of TH in ARDS patients who are receiving neuromuscular blockade (NMB) as supportive care. Since the shivering response of all randomized patients will be abrogated, this study design facilitates cooling and avoids differences in anti-shivering drug use, including NMB, between the TH and control arms of the study. Our recent pilot study supports both the feasibility for this investigative strategy and the likelihood that TH will be beneficial in patients with ARDS. This single-center pilot RCT is designed as the next step to develop the infrastructure and generate high quality data about effect size of TH on mortality and surrogate outcomes to inform design of a larger and more definitive multicenter trial. The trial will be conducted in three intensive care units (ICUs) at the University of Maryland Medical Center (UMMC), the medical intensive care unit (MICU), cardiac care unit (CCU), and the Critical Care Resuscitation Unit (CCRU). To facilitate randomization within the inclusion window, we will consent and enroll based on partial fulfillment of randomization criteria and randomize once the final criteria are met. Patients with ARDS and P/F ratio \( \leq 200 \) (while on \( \geq 5 \) cm H\(_2\)O PEEP and \( \geq 0.6 \) FiO\(_2\)) for \( <48\)h will be offered enrollment but will not be randomized until P/F ratio is \( \leq 150 \) (while on \( \geq 5 \) cm H\(_2\)O PEEP and \( \geq 0.6 \) FiO\(_2\)) and the patient is receiving or ordered to receive NMB by the ICU team. We plan to randomize a total 32 patients over 4 years to hypothermia (core temperature 34°-35°C for 48h) or usual temperature management. The primary outcome measure will be 28-day ventilator-free days (VFDs). Secondary outcomes will include 28-day ICU-free days, oxygen saturation index, driving pressure, Sequential Organ Failure Assessment (SOFA) score, 60- 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. This pilot RCT is designed to provide critical information to plan a definitive multicenter Phase IIb or Phase III RCT of therapeutic hypothermia in patients with ARDS and receiving NMB by: (1) analyzing the enrollment and randomization rates based on optimized inclusion and exclusion criteria and enrollment and randomization protocols; (2) developing essential study infrastructure, including subject randomization and data management, designed to rapidly transition to web-based methods that will support a multi-center trial; (3) optimizing and validating protocols for ventilator and fluid management; (4) estimating the beneficial effect and safety of mild TH (34-35°C for 48h) in patients with ARDS and P/F < 150 receiving NMB; and (5) optimizing Adverse Event reporting in the CHILL patient population. We expect this single-center Phase IIb pilot RCT of TH in ARDS to establish the necessary infrastructure for and provide sufficiently definitive information to design and execute a multicenter Phase IIb or Phase III RCT of TH in ARDS. This pilot trial will use paper case report forms (CRFs) developed to
rapidly transition to electronic on-line forms, an individual Data Safety Monitor (Dr. Avelino Verceles), and in-house randomization and data management.

1.2 Study Aims and Objectives
We will conduct the CHILL-pilot single-center RCT of TH in patients with ARDS and P/F<150 who are receiving NMB to address the following specific aims:

1. **Analyze the enrollment and randomization rates based on optimized inclusion and exclusion criteria and enrollment and randomization protocols.** The real-world enrollment and randomization rates from this pilot study will be the basis determining the size and duration of the follow-up multicenter trial.

2. **Develop essential study infrastructure, including subject randomization and data management, designed to rapidly transition to web-based methods that will support a multi-center trial.** All study forms and protocols will be designed in consultation with Axio Research LLC to facilitate rapid migration to electronic web-based randomization and data management methods required for the follow-up multicenter trial.

3. **Optimize and validate protocols for ventilator and fluid management.** Develop and validate a fluid management protocol relevant for the CHILL target population, including patients with and without central venous pressure measurements and patients with renal failure.

4. **Estimate the benefit and safety of mild TH (core temperature 34°-35°C for 48h) in patients with ARDS and P/F <150 receiving NMB.** We will evaluate multiple outcomes, including 28-day VFDs (primary), 28-day ICU-FDs, day-3 driving pressure and oxygen saturation index (OSI), circulating levels of proinflammatory mediators, Sequential Organ Failure (SOFA) scores, and the known consequences of therapeutic hypothermia for fluid/electrolyte balance, hemodynamics, and coagulation.

5. **Optimize Adverse Event reporting in the CHILL patient population.** The protocol will balance efficiency and effectiveness of capturing clinically meaningful adverse events.

We expect this single-center Phase IIb pilot RCT of TH in ARDS to establish the necessary infrastructure for and provide sufficiently definitive information about effect size and variability to design and execute a multicenter Phase IIb or Phase III RCT of TH in ARDS.

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.

As a first step to analyzing the benefit of TH in ARDS, we completed a historically controlled open-label pilot study that addressed the feasibility of studying TH in ARDS patients receiving NMB. Our retrospective review of 58 patients with ARDS (P/F <150) receiving cisatracurium in the University of Maryland Medical Center (UMMC) Medical Intensive Care Unit (MICU) from 2012-15 showed that NMB alone did not cause hypothermia or prevent fever. The review identified continuous renal replacement therapy (CRRT) as a confounder that caused unintentional hypothermia during NMB, which the CHILL-pilot addresses in its temperature management protocols (see Interventions). Our open-label pilot study of TH in 8 consecutive NMB-treated ARDS (P/F <150) patients demonstrated feasibility of maintaining TH in this population. Target temperature was reached within 4h and maintained for 92% of the 48h cooling period using Cincinnati Sub-Zero Blanketrol™ II cooling blankets (6 patients) and the Artic Sun™ system (2 patients). Cooling and rewarming were well tolerated without serious adverse events (SAEs). Comparison with historical controls, who had similar ARDS severity and received NMB without cooling, showed that median (interquartile range/IQR) core temperature was 2.3°C lower in the cooled patients than controls (34.4 (34.3-36.7)°C vs. 36.65 (36.3-37.3)°C; p<0.0001). When compared to historical controls, the cooled patients showed trends toward reduced hospital mortality (25% vs. 53.4%, p=0.26), higher 28-day VFDs (9 (0-21.5) vs. 0 (0-12), p=0.16), and higher day 3 P/F ratio (255 (160-270) vs. 171 (120-214); p = 0.024). Since all patients were treated using ARDSNet ventilator and fluid management protocols and NMB, these results suggest TH during the first 48h of ARDS may confer benefit that is additive with current therapy.

1.4 Abbreviations and Acronyms
CHILL: Cooling to Help Injured Lungs
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
2 Study Organization and Staff Roles and Responsibilities

2.1 Participating Centers

2.1.1 Organizational Chart

2.1.2 Study Center

2.1.2.1 Study Units
UMMC Medical Intensive Care Unit (MICU)
UMMC Cardiac Care Unit (CCU)
UMMC Critical Care Resuscitation Unit (CCRU)

2.1.2.2 Clinical Operations Core (CC)
The Clinical Operations Core (CC) will be headed by Carl Shanholtz, MD
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.

2.1.2.2.1 Specific Responsibilities of the CC:
1. Establish and maintain subcontracts with UMMC for study-related clinical costs
2. Disburse payments to UMMC for study-related lab tests and cooling supplies
3. Collect and maintain all regulatory documents (curricula vitae, CITI GCP certifications,
   CITI human subjects research, clinical lab CLIA certification and normal ranges).
4. Provide training to all clinical personnel regarding GCP, screening and clinical protocols.
5. Develop and maintain all study protocols and standard operating procedures regarding
   patient screening and clinical protocols and collecting and handling research samples.
6. Maintain real-time tracking and correction of clinical protocol noncompliance
7. Establish and manage the IRB approval
8. Report adverse events to IRB, DC, and DSMB
9. Maintain continuous monitoring of data quality
10. Monitor human subject protection
11. Manage the CHILL-pilot record in Clinicaltrials.gov
12. Monitor enrollment for meeting timing and budgetary milestones
13. Prepare annual reports and other necessary communication with NHLBI
14. Maintain oversight of biomarker core

2.1.3 Data Management

2.1.3.1 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. Dr. Terrin will consult with Axio Research LLC to ensure that the in-house protocols are consistent with future migration to electronic on-line randomization and data management services to be provided by Axio for the follow-up multicenter trial.

2.1.3.1.1 Specific Responsibilities of the DC:
1. Maintain oversight of the Randomization and Data Management Core, including the computer-based CHILL treatment assignment tool.
2. Communicate with DSMB, including preparation of summaries for semi-annual DSMB meetings.
3. Provide instruction and training to clinical personnel regarding randomization and data management processes, procedures, and metrics.
4. Perform database back-up and post-study database lock.

2.1.4 Laboratories

2.1.4.1 The Biomarker Core (BC)

The Biomarker Core will be directed by Jeffrey Hasday, MD

2.1.4.1.1 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.

2.1.4.1.2 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-1β, 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, Shanhoitz, 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. Shanhoitz. 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. These activities will be reviewed with Axio Research, LLC by Dr. Terrin to ensure compatibility with future migration to the Axio electronic on-line platform.

#### 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. Dr. Terrin will conduct bi-monthly conference calls with Ms. Anna Leonen, Axio Research LLC, to discuss compatibility of CHILL study protocols with the Axio platform.

2.2.2 Funding Agency
The initial phase of this pilot RCT is self-funded. A grant has been submitted to the NIH for funding via the R34 mechanism.

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. Shanboltz is Leader of the Clinical Operations Group. Responsibilities include:
1. Dr. Shanboltz 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 MPs 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. Jennifer McGrain, RRT is the lead study coordinator and will oversee a coordinator team that includes Drs. Andrew Deitchman, Diana Amariei, and Neal Dodia. 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 18-80 years old in a study ICU 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.

1. The CHILL screening log is stored on the UMB Microsoft OneDrive:
   a. Open CHILL_Screening_Log_1.2.xlsm to run in the local Excel program by clicking on 3 vertical dots next to the file title, clicking on “Open” and then on “Open in Excel” with macros activated.
   b. Select Tab 3 to view the Screening handoff tool. Enter date, time and your name (from pulldown menu) in indicated fields, update the census by deleting patients who have been transferred/discharged from the ICU, and adding newly admitted patient, and update the patient study status from the pulldown menu. A “never eligible” status means the patient will never be eligible for enrollment in CHILL because of age or exceeding the mechanical ventilation 7-day window and need not be followed.
   c. For patients who meet the age and mechanical ventilation criteria for enrollment, enter their information and obtain study ID numbers by clicking on Tab 2 and Pushing the “Start” button.
   d. Enter your name (from Pull-down menu), the patient’s name and MRN number, the Unit where they are currently located (from the pulldown menu), and the room number. If the final status (excluded or enrolled) is known enter the status and if excluded the reason for exclusion from the pulldown menus. If you do not know the final status at the time of initial screen, you can enter it at a later time as described below. Push the “Push button for study number and ID” button. The
patient’s study number and 3-letter ID are displayed below. If any information is missing you will be cued to enter it. All information along with a date and time stamp will be recorded on Sheet 1, which is locked. Contact Dr. Hasday in case of an error in data entry.

e. To enter final status (and if applicable reason for exclusion) for patients who already have a study ID number/3-letter identifier, Push “Push to Start” button at the top of the spreadsheet, then enter 3-digit number and 3-letter identifier in CAPS in B14 and B15, the final status, and if applicable the reason for exclusion from the pulldown menus and push the “Push button to enter final status” button. If the 3-digit number and 3-letter identifier match you will get a message the final status has been recorded. Otherwise you will get a message that the 3-digit number and 3-letter identifier do not match. In this case make sure the letters are all in CAPS and that you have entered both correctly and push the button again. The final status and if applicable the reason for exclusion will be recorded on Sheet 1.

3.2 Enrollment

3.2.1 Inclusion Criteria
1. men and women
2. any race/ethnicity
3. 18-80 years of age
4. endotracheal tube or tracheostomy in place and mechanically ventilated;
5. P/F <200 with PEEP ≥5 cm H2O
6. radiologic evidence of bilateral pulmonary infiltrates
7. access to an LAR to provide consent.
8. Criteria 3 and 4 must be met within 48h of enrollment (and randomization), not be fully explained by hydrostatic pulmonary edema, and must have occurred within 7 days onset of a condition associated with ARDS.

3.2.2 Exclusion Criteria
1. Missed ARDS window (>48hrs)
2. Missed NMB window: (>12 hrs)
3. Missed mechanical ventilation window (>7 days)
4. Refractory hypotension (> 0.2 mcg/kg/min of norepinephrine or equivalent dose for minimum of 6 h)
5. Core temperature <35.5°C while not receiving CRRT
6. No Legally authorized representative available
7. Significant, active bleeding (>3u blood products and/or surgical/IR intervention)
8. Platelets <10K/mm³ (uncorrected)
9. Active hematologic malignancy
10. Skin process precludes cooling device
11. Moribund, not likely to survive 72h
12. Pre-morbid condition makes it unlikely that patient will survive 28 days
13. Do Not Resuscitate status
14. Not likely to remain intubated for ≥48h
15. Physician unwilling to participate
16. Severe underlying lung disease
   a. On home O₂
   b. On BIPAP (except for OSA)
   c. Prior lung transplantation
17. BMI >45 kg/m²
18. Known NYHA class IV heart disease
19. Acute Coronary Syndrome past 30 days (MI, unstable angina)
20. Cardiac arrest within 30 days of enrollment
21. 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 criteria at time of randomization
1. have P/F <150 with PEEP ≥5 cm H₂O
2. be currently receiving deep sedation and NMB agents for ≤12h or have orders written to administer deep sedation and NMB agents
3. plan to remain on NMB for at least two additional days.

3.3.2 Randomization Procedures
Prior to CHILL-Pilot receiving external funding and Axio Research, LLC participation the randomization will be performed using the CHILL Treatment Assignment Tool:
2. Randomization will be performed by a macro-driven Excel spreadsheet stored on the UMB Microsoft OneDrive:
   a. CHILL_Assignment_Tool 2.6.xlsm
   b. Randomization schedules for 50 pruned and 50 unpruned patients have been loaded into the assignment tool and password-protected. Dr. Brown and Ms. Susan Holt (Biostatistics Division Administrator)
   c. Location of the file is on a MS OneDrive (cloud-based), restricted-access shared file.
3. Log onto UMB MS OneDrive
4. Open CHILL_Assignment_Tool_2.6_loaded.xlsm
5. Select run on Excel on local computer
6. Press “Push to Start” button
7. Enter investigator name from pull down menu and press “Push to Start” button again
8. Enter patient’s Study ID number and press “Push to Start” button again
9. Confirm by reentering Study ID number and press “Push to Start” button again
11. Enter proning status using pulldown menu and press “Confirm Proning Status, Then Push this Button to Get Assignment” button.
12. The assignment will be displayed as “COOL” or “CONTROL.”
13. Record assignment and exit program.
14. The program saves the patient study number and 3-letter ID, date, time, investigator, and treatment and remains locked and password protected.

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 Shan Holtz, 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 Shan Holtz or a Clinical Team member.

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 a
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 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 Shanholzt 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, CCU, CCRU) who are 18-80 years old 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 worksheet 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-letter patient identifier will be supplied by the online 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 online 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. If consent is obtained, the patient will be enrolled and the “Yes” box about consent 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
Those patients who meet enrollment criteria and for whom consent is obtained will be assigned a study number, including a 2-letter site (“UM” for University of Maryland) and a 3-digit number assigned in order of patient enrollment. The site and study number and the patient’s 3-
letter identification from the screening form will be recorded on the enrollment form. A note about the enrollment will be placed in the Electronic Medical Record and the appropriate box checked. Additional information about date/time that ARDS criteria have been met and duration and type of artificial airway, and qualifying P/F ratio will be recorded. The patient will then be evaluated for randomization using the Randomization Worksheet.

6 Randomization Procedures
If the patient meets criteria for randomization within the inclusion window (48 hours for ARDS and 12 hours for NMB), they will be randomized and the “Yes” box about randomization will be checked on the Randomization CRF and the date and time of randomization, proning status at time of randomization, the treatment assignment and the name of the investigator who makes the assignment will be recorded. Otherwise the “No” box and the box indicating reason for not being randomized will be checked. 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. A randomization table of 50 assignments has been generated for each of the prone and unproned patients. Assignment will be made using the CHILL Treatment Assignment Tool. Once Randomized, baseline information will be recorded on the Baseline Data CRF and, if assigned to the Therapeutic Hypothermia arm, cooling will begin as soon as possible.

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

<table>
<thead>
<tr>
<th>DAYS</th>
<th>-2</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>7</th>
<th>8-27</th>
<th>28</th>
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<th>Hospital DC</th>
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<tbody>
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<td></td>
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<td></td>
<td>X</td>
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<td>Pregnancy test (F)</td>
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<td>X</td>
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<tr>
<td>Randomization, baseline data, start assigned temperature management</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Q2h vital signs (e.g. SpO2, mean airway pressure, core temperature)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Basic metabolic panel, CBC (times per day)</td>
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<td>Ventilator and respiratory parameters</td>
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<td>X</td>
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<td>X</td>
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<td>ICU DC</td>
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<tr>
<td>Monitor for AEs</td>
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<td>X</td>
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<td>X</td>
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<td>X</td>
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<td>X</td>
<td></td>
<td>ICU DC</td>
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<tr>
<td>Calculation 28-day VFDs, ICU-FDs</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>ICU DC</td>
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<tr>
<td>MOCA</td>
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<td>X</td>
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<td></td>
<td>ICU DC</td>
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<tr>
<td>Assess Vital and functional status</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>ICU DC</td>
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<td></td>
</tr>
</tbody>
</table>

X = Required (time not specified)
A = When Available
8 Study Measurements

8.1 Vital signs
Vital signs will be recorded from data on flowsheets in the EMR. The data will be obtained from the nurse at the bedside who is not part of the study team.

8.1.1 Heart rate
Heart rate will be obtained by EKG telemetry monitoring in the ICU (GE Healthcare).

8.1.2 Blood Pressure
Blood pressure will by either non-invasive automated cuff (Critikon, GE Healthcare) or arterial catheterization transduced by the patient monitoring system (GE Healthcare). In the case that both types of monitoring are present invasive arterial monitoring will be preferentially recorded.

8.1.3 Respiratory rate
Respiratory rate will be recorded by the bedside monitor using impedance transduction from the EKG leads (GE Healthcare). In the event of artifact due to ineffective respirations or patient movement the respiratory rate will be recorded from the ventilator (Servo-I, Maquet, or Evita V500, Draeger). In the event this respiratory rate is also deemed inaccurate due to ventilator dyssynchrony or breath stacking the respirations will be counted manually for 30 seconds.

8.1.4 Pulse oximetry
Pulse oximetry will be recorded by Nellcor or Masimo sensors transduced by the GE Healthcare monitor. Sensor will be placed on the finger, earlobe, or forehead as necessary to obtain and adequate pulse signal.

8.2 Core temperature
Core temperature will be measured from esophageal or rectal probes, temperature sensing bladder catheters, or pulmonary artery catheters, if present. If a pulmonary catheter is present temperature readings from the thermistor will be preferentially recorded. If no catheter or temperature probe is present and esophageal temperature probe will be placed.

8.3 Ventilatory and respiratory parameters
Ventilatory and respiratory parameters will be measured from the graphic display on the ventilator (Maquet Servo-i or Draeger Evita V500) by the unit respiratory therapist who is not part of the study team and recorded in the ventilator care flowsheet in the EMR.

8.3.1 Peak inspiratory airway pressure (Ppeak)
Peak airway will be captured from the digital display on the ventilator at end-inspiration during a breath without spontaneous ventilatory effort.

8.3.2 Airway Plateau pressure (Pplat)
Plateau pressure will be captured from the digital display on the ventilator after a 0.5 second end-inspiratory pause with both inspiratory and expiratory valves held closed during a breath without spontaneous ventilatory effort.
8.3.3 Positive end-expiratory pressure (PEEP)
Because patients will be ventilated with a ratio of inspiratory time: expiratory time less than 1:1 (i.e. not inverse ratio) PEEP recorded will be the applied PEEP set on the ventilator unless otherwise noted.

8.3.4 Driving pressure
Driving pressure will be calculated as the difference between airway plateau pressure and end-expiratory pressure (Pplat – PEEP) during a breath without spontaneous ventilator effort.

8.3.5 Mean Airway Pressure (P\textsubscript{aw})
Mean airway pressure will be captured from the digital display on the ventilator during a breath without spontaneous ventilatory effort.

8.3.6 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\textsubscript{aw} × FiO\textsubscript{2} × 100/SpO\textsubscript{2})

8.4 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.

8.5 Fluid management
Fluid intake and output (I/O) will be recorded in the EMR by the patient’s nurse who is not part of the study team. I/O totals are computed every 24 hours from 0700-0659 and fluid will be managed by the primary ICU providers based on the following protocol.

8.5.1 Fluid management protocol:
**Fluid management** (excluding patients in shock): In subjects who are not in shock, a conservative fluid management approach will be required (see Table below). This conservative fluid management approach will represent a simplification of the algorithm utilized in the ARDS Network FACTT study\textsuperscript{10}. 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 renal failure

Guidelines for Fluid Management

<table>
<thead>
<tr>
<th>CVP^a</th>
<th>PAOP (optional)</th>
<th>MAP &gt; 60 mm Hg AND off vasopressors for &gt; 12h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8^b</td>
<td>&gt; 12^b</td>
<td>Average urine output &lt; 0.5 ml/kg/hr</td>
</tr>
<tr>
<td>4-8^c</td>
<td>8-12^c</td>
<td>Furosemide^e</td>
</tr>
<tr>
<td>&lt; 4^d</td>
<td>&lt; 8^d</td>
<td>Reassess in 1h</td>
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<tr>
<td></td>
<td></td>
<td>Average urine output &gt; 0.5 ml/kg/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Furosemide^e</td>
</tr>
<tr>
<td></td>
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<td>Reassess in 4h</td>
</tr>
<tr>
<td></td>
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<td>Give fluid bolus</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>No intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reassess in 4h</td>
</tr>
</tbody>
</table>

^aIf 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 euveolemic (CVP 4-8 or PAOP 8-12).

^bIf no CVC, PICC, or PAC present, can substitute distended IVC on bedside ultrasound or elevated NT-proBNP (adjusted for age)

^cIf 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 euveolemic.

^dIf no CVC, PICC, or PAC present, can substitute collapsible IVC on bedside ultrasound

^eRecommended 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.

8.6 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.

9 Study Interventions
Neuromuscular blockade: Since treatment with NMB is a criterion for randomization, subjects in both arms will have already been receiving sedation with RASS -5 and NMB for 0-12h at randomization. In accordance with institutional protocol for NMB, the cisatracurium in both study arms will be 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) in the TH arm and for at least 54h post-
randomization in controls. NMB will then be discontinued unless the ICU team feels there is clinical indication for continued NMB (e.g. ventilator dyssynchrony). We will collect data about cisatracurium infusion rate and duration, train-of-four responsiveness, time-to-recovery from NMB, and incidence of ICU myopathy in both arms, which will be used in planning the follow-up multicenter trial. Criteria for stopping NMB early are sustained severe bradycardia (heart rate < 30 associated with mean arterial pressure <65 without vasopressor agents) and unexplained anaphylaxis.

Temperature management:

1. Therapeutic Hypothermia Arm: The participating ICUs share an established institutional protocol for TH, which will facilitate rapid mobilization of treatment following randomization. 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: If patient randomized to hypothermia arm, have a member of the MICU provider team enter the UMMC MED-CC Hypothermia Following Arrest Supplemental order set in Epic with the following modifications:

- 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, cisatracurium.
- Under Chemistry, select Comprehensive Metabolic Panel
- Modify Hyper/Hypothermia order by changing stop date from 24h to 48 h and changing comments to: “Lower patient’s temperature to 34 – 35°C as quickly as possible per protocol. Maintain core temperature between 34 and 35°C for 48 hours. AT 48 hrs after the initial cooling, re-warm patient no faster than 0.3 degree C per hour to 36°C.” Delete “Then maintain ≤ 37°C 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 the same sedation, NMB, and monitoring as the TH arm. During the 54h post-randomization period (corresponding with cooling and re-warming 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.
10 Case Report Forms
Appended.

11 Question by Question (QxQ) Instructions
11.1 Screening worksheet

- 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 if patient is 18-80 years old by checking the appropriate “Yes/No” box on line 3.
- Indicate if patient has been intubated for <7 days or, if the patient has a tracheostomy, has been mechanically ventilated for <7 days by checking the appropriate “Yes/No” box on line 4.
- If the answers on lines 3 and 4 are both “Yes,” indicate all applicable exclusion criteria under line 5 by checking the appropriate boxes.
- If the answer on line 3 or 4 is “No” or any of the listed exclusion criteria on line 5 are present, the patient is not eligible for the study; complete the Screening CRF.
- If the answers on line 3 and 4 are both “Yes” and none of the exclusion criteria on line 5 are present, proceed with the Berlin criteria checklist. Indicate whether one of the listed ARDS risk factors on line 6 was present within 7 days of onset of acute respiratory failure by checking the appropriate yes/no box on line 6 and indicate all applicable risk factors. If none of the ARDS risk factors apply, check the “No” box, patient is not eligible for CHILL; complete the Screening CRF.
- If the answer on line 6 is “Yes,” indicate the time and date of each screen (line 7), and check the appropriate “Yes/No” box for each criterion: (a) whether bilateral pulmonary infiltrates are present on chest x-ray or chest CT scan (line 8), (b) whether based on available clinical, physiological, and echocardiographic data you can exclude cardiogenic cause as the sole etiology (line 9); (c) whether the qualifying P/F ratio was measured with PEEP≥5 cm H2O (line 10); (d) whether P/F<300 (line 11); or whether P/F<200 (line 12). If the answer to all questions about Berlin criteria is “Yes,” the patient is eligible for enrollment; fill out Enrollment CRF. If the answer to one or more questions about Berlin criteria, continue to screen the patient at appropriate intervals, recording the time and date of each screen and checking the applicable “Yes/No” box for each criterion that the patient failed to meet on prior screens. Check the N/A box for all criteria that the patient met on prior screens. If patient meets all Berlin criteria within 7 days of onset of intubation/mechanical ventilation, within 48 hours of meeting ARDS criteria (including P/F <300), and within 12 hours of starting NMB, the patient is eligible to enroll; Check the “Yes” box online 13 and complete the Screening and Enrollment CRFs. Otherwise, check the “No” box on line 13 and complete the Screening CRF.
- Record patient name and Medical record number in section 14 (This must remain secure).
11.2 Screening CRF
- 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.
- Record your name and date and time of form completion in indicated fields on line 1.
- Record date and time the patient was first screened in indicated fields on line 2.
- Indicate location of patient at time of final screen on line 3.
- Indicate gender of patient by checking the appropriate box on line 4.
- Indicate patient’s date of birth in indicated field on line 5
- Indicate whether Hispanic/Latino by checking the appropriate box on line 6.
- Indicate the single most accurate description of patient’s race by checking the appropriate box on line 7.
- Indicate whether the patient was offered enrollment by checking the appropriate “Yes/No” box on line 8 and, if “No,” indicate all relevant reasons why enrollment was not offered by checking the Yes or No boxes for all potential reasons below.
- If the patient was offered enrollment, indicate whether the patient or their LAR consented to the patient’s participation in the study by checking the appropriate “Yes/No” box. If “Yes,” complete the Enrollment CRF.

11.3 Enrollment CRF
- Record site ID code (01 for UMB), a unique 3-letter patient identifier (e.g. patient initials), and the next assignable 3-digit study ID in the indicated fields at the top of each page.
- Record the date and time CRF was completed in the indicated field in line 1 and your name on line 2.
- Record the date and time that signed consent was obtained in the indicated field on line 3.
- Make sure that a signed enrollment note is placed in patient’s bedside chart and was submitted to be scanned for the Electronic Medical Record and check the “Yes” box on line 4 and record the time and date of the note in the indicated field.
- Indicated the date and time when all criteria for ARDS and P/F <200 were met in the indicated field on line 5.
- Indicate type of initial qualifying imaging study (CXR or CT) by checking the appropriate box on line 6 and record the date and time of the study in the indicated field. Indicate the number of lung quadrants with opacities by checking the appropriate box on line 7.
- Record the date and time that patient began continuous (<24 hours interruption) mechanical ventilation on line 8.
- Indicate the type of artificial airway present at time of enrollment by checking the appropriate box on line 9.
- If the patient had a tracheostomy at time of enrollment, indicate whether it was place within 30 days of enrollment by checking the appropriate box on line 10.
- If the patient was intubated at enrollment, record time and date of intubation in the indicated field on line 11.
- Record the value and date and time of the qualifying P/F ratio (<200) on lines 12 and 13, respectively.
11.4 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.

11.5 Randomization worksheet
- 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 the date and time worksheet was initiated in the indicated field in line 1 and your name on line 2.
- Record date and time that all criteria for ARDS were first met (P/F < 300) on line 3.
- Record date and time that patient began continuous mechanical ventilation on line 4 with ≤24h interruption).
- Indicate whether NMB was started by checking appropriate “Yes/No” box and, if “Yes,” record date and time when it first started (if infusion was interrupted, record date and time it was initially started) on line 5.
- Record date and time that randomization window closes on line 6 (7 days after initiation of ARDS-associated underlying disorder; 7 days after initiation of mechanical ventilation; 48 hours after ARDS criteria first met, or 12 hours after NMB first started, whichever comes first)
- Use checklist following line 7 to track whether randomization criteria have been met by recording the date and time of each randomization evaluation and the appropriate “Yes/No” box under each criterion. Record the P/F ration for each evaluation on the indicated line.
- Indicate whether randomization criteria have been met by checking the appropriate “Yes/No” box on line 8 and, if Yes, record the date and time criteria were met
- If “No,” indicate all reasons why patient was not randomized on line 9 (check all that apply).
- Complete Randomization CRF.

11.6 Randomization 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 whether the patient was randomized by checking the appropriate “Yes/No” box on line 2.
- If “Yes,” indicate time and date of randomization in the indicated fields on line 3 and complete questions 4 – 6. If “No,” skip to line 7 and indicate the reason(s) the patient was not randomized by checking all appropriate boxes.
- Indicate the whether the patient was receiving prone positioning at time of randomization by checking the appropriate “Yes/No” box on line 4.
- Indicate to which treatment arm the patient was assigned checking the appropriate box on line 5.
• Indicate the investigator who made the assignment on line 6.
• If patient was not randomized indicate all reasons (check Yes or No for all boxes) on line 7.
• List home and cell phone numbers and email addresses for patient where indicated on line 8. List name and contact information for the Legally Authorized Representative (LAR) who signed the CHILL-pilot study consent form. List the names, relationship with the patient, and contact information for potential contacts who can provide information about the patient’s vital and functional status at the 60- and 90-day telephone follow-ups.

11.7 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 hospital admission 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. Only record peripheral temperatures if there were no core temperatures measured. 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 SpO2 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 PaO2, including the pH, PaCO2, the PaO2, and the corresponding FiO2 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 H2O in the appropriate fields on line 19.
- Enter the respiratory rate in breaths per minute and PEEP in cm H2O 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 P1/ high, P2/PEEP in cm H2O and the T1/ high and T2/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 H2O and the corresponding FiO2 and PEEP, the peak inspiratory pressure and mean airway pressure in cm H2O 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 24, record the post-change parameters.
- 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 H2O, and body temperature in ºC prior to randomization in the indicated fields beginning on line 25. Convert ºF to ºC using the following formula:

ºC = (ºF – 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.
- Indicate the Date and Time NMB was started in the appropriate fields on line 30.
- If a proning protocol has been initiated, indicate the time and date the protocol was initiated in the appropriate filed on line 31. 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 32, indicate the cooling method used by checking the appropriate box on line 33. If the patient is in the Usual Temperature Management group, write “NA” in the month field on line 32.
- Indicate whether the baseline research blood sample was collected by checking the appropriate Yes/No” box on line 34.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 35.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 36.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 37.
- 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 38.

11.8 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 and, if “No,” record date and time it was discontinued in the indicated fields, check the appropriate box for the major reason it was discontinued on line 6 (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 7 or check the “No” 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 8. If “No” skip to question 11. 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 9. Indicate whether the patient is still being cooled as of 0800 of study day 1 by checking the appropriate “Yes/No” box on line 10. If “Yes” skip to question 12. If “No,” record date and time cooling was stopped in the indicated fields and indicate the most closely applicable reason for discontinuing 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 11. 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 12 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 13. 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 14. If the patient was not previously receiving RRT, check the N/A box.

- On line 15, 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 16. 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 17 enter for each 2-hour period beginning at time of randomization and continuing until 0800 on the day after randomization the highest and lowest recorded core temperatures, check the box next to the location of the probe, and enter the lowest recorded SpO2 value, the corresponding FiO2, 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 SpO2 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 since randomization by checking the appropriate “Yes/No” box on line 18. 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 19. 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 20. 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 21.
• Beginning on line 21, 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 22, 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.
• Indicate all ventilator modes used since randomization by checking the appropriate boxes under line 23 and circle the mode used at 0800.
• Indicate whether the patient was extubated since randomization by checking the appropriate “Yes/No” box on line 24 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 25.
• 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 26.
• Enter the highest and lowest PEEP and Mean airway pressure in cm H2O during mechanical ventilation since randomization in the appropriate fields on lines 27 and 28, 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 29. 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 PaO2 and associated FiO2 since randomization in the appropriate fields on line 30. 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 31.
• Record the total output (including net volume removed by RRT) between randomization and 0800 in the field on line 32.
• Indicate whether the day 1 research blood sample was collected by checking the appropriate “Yes/No” box on line 33.
• Record the date and time the research blood sample was collected and processed in the appropriate fields on line 34.
• Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 35.
• Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 36.
• 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 37.

11.9 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 in the indicated fields, check the appropriate box for the major reason it was discontinued on line 6 (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 7 or check the “no” box if neuromuscular function did not return through day 28.
• Indicate whether the patient is in the hypothermia by checking the appropriate “Yes/No” box on line 8. If “No” skip to question 10. 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 9. If “Yes” skip to question 11. If “No,” record date and time cooling was stopped in the indicated fields and indicate the most closely applicable reason for discontinuing 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 10. 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 11 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 12. 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 13. If the patient was not previously receiving RRT, check the N/A box.
• On line 14, please 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 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 16 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 SpO2 value, the corresponding FiO2, 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 SpO2 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 17. 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 18 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 19. 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.
- 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.
- In the appropriate fields in table beginning on line 21, 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 2 (or 3) skip to question 29.
- 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 22 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 23 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 24.
- 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 25.
- Enter the highest and lowest PEEP and Mean airway pressure in cm H2O in the last 24 hours in the appropriate fields on lines 26 and 27, 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
28. 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 PaO2 and associated FiO2 since randomization in the appropriate fields on line 29. 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.
- Enter total intake in ml in the field on line 30.
- Enter total output (including net volume removed by RRT) in the last 24 hours in the field on line 31.
- Indicate whether the research blood sample was collected by checking the appropriate “Yes/No” box on line 32.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 33.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 34.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 35.
- 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 36.

11.10 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 in the indicated fields, check the appropriate box for the major reason it was discontinued on line 6 (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 7 or check the “no” box if neuromuscular function did not return through day 28.
- Indicate whether the patient is in the hypothermia by checking the appropriate “Yes/No” box on line 8. If “No” skip to question 10. If “yes” indicate whether the patient completed 48 hours of hypothermia by checking the appropriate “Yes/No” box on line 9. If “Yes” skip to question 11. 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 10. 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 11 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 12. 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 13. If the patient was not previously receiving RRT, check the N/A box.

• On line 14, 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 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 16 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 SpO2 value, the corresponding FiO2, 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 SpO2 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 17. 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 18. 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 19. 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.

• 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.

• In the appropriate fields in table beginning on line 21, 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 29.
- 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 22 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 23 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 24.
- 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 25.
- Enter the highest and lowest PEEP and Mean airway pressure in cm H₂O in the last 24 hours in the appropriate fields on lines 26 and 27, 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 28. 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 PaO₂ and associated FiO₂ since randomization in the appropriate fields on line 29. 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.
- Enter total intake in ml in the field on line 30.
- Enter total output (including net volume removed by RRT) in the last 24 hours in the field on line 31.
- Indicate whether the research blood sample was collected by checking the appropriate “Yes/No” box on line 32.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 33.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 34.
- Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 35.
- 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 36.

11.11 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 in the indicated fields, check the appropriate box for the major reason it was discontinued on line 6 (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 7 or check the “no” box if neuromuscular function did not return through day 28.
• 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 8.
• 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 9 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 10. 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 11. If the patient was not previously receiving RRT, check the N/A box.
• On line 12, 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 13. 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 14 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 SpO2 value, the corresponding FiO2, 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 SpO2 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: \( \text{FiO2} = 0.21 + 0.03 \times \text{flow rate in LPM} \).
• Indicate whether the patient received corticosteroids in the last 24 hours by checking the appropriate “Yes/No” box on line 15 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 16. 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 17. 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 18.
- Beginning on line 18, 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 19, 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 27.
- Indicate all ventilator modes used in the last 24 hours by checking the appropriate boxes under line 20 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 21 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 22.
- 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 23.
- Enter the highest and lowest PEEP and Mean airway pressure in cm H₂O in the last 24 hours in the appropriate fields on lines 24 and 25, 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 26. 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 PaO2 and associated FiO2 since randomization in the appropriate fields on line 27. 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 28.
- Record the total output (including net volume removed by RRT) in the last 24 hours in the field on line 29.
- Indicate whether the research blood sample was collected by checking the appropriate “Yes/No” box on line 30.
- Record the date and time the research blood sample was collected and processed in the appropriate fields on line 31.
- Indicate how many 0.5 ml aliquots from the sample by checking the appropriate box on line 32.
• Record the time and date the samples were placed in the -80°C freezer in the appropriate field on line 33.
• 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 34.

11.12 Unassisted Breathing CRF
• 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 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. 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.

11.13 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.
• Enter name of individual who completed data entry for the ICU-free period and date/time of completion in the appropriate fields on lane 8.
• 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 9 and record the date and time of cancellation/readmission on line 10.
• 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 11.
• For each readmission please use the subsequent ICU discharge checklist with the same instructions as above

11.14 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.

11.15 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.

11.16 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.
11.17 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.

11.18 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.

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

12.1.1.1 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.

12.1.1.2 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

12.1.1.3 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.

12.1.1.4 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.

12.1.1.5 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
12.1.2 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 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). Seven milliliters EDTA-anticoagulated blood will be collected in one purple-top Vacutainer™ tube on each of study days 0-4 and 7 and will be transported on ice to the Hasday laboratory for processing and storage within 30 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 CO₂ 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 that will be converted to electronic on-line CRFs by Axio Research, LLC during the R31/66-funded phase. CC clinical staff (Drs. Hasday and Shanboltz, the 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. Once R31/66 funding begins, data will be entered into the MERGE clinical™ electronic data capture (eDC) system within 24h. CC clinical staff will be certified with staff ID numbers based on tests of study-specific knowledge and performance. Only certified clinical staff will be able to log onto the eDC system to enter data, and each data item will be traceable back to the individual responsible for it. Data entry on the eDC will include checks for data type (e.g., alpha versus numeric) and range for each item with pop-up error notifications. Consistent with the pace of patient enrollment, the DC will run delinquent form, specimen status, cross form and Boolean logic checks on the database monthly, and a monthly summary report prepared for discussion at CEC meetings. For each of the bi-annual DSMB reports and each publication, the DC will extract a data analysis file from the database and archive that data analysis file for the duration and at least two years following the end of the clinical trial.

14 Quality Assurance Procedures
APPENDIX

CHILL Pilot Case Report Forms and Worksheets:

1. Screening Worksheet
2. Screening CRF
3. Enrollment CRF
4. Enrollment Note
5. Randomization Worksheet
6. Randomization CRF
7. Baseline Data CRF
8. Day 1 Data CRF
9. Day 2 Data CRF
10. Day 3 Data CRF
11. Day 4 Data CRF
12. Day 7 Data CRF
13. Unassisted Breathing CRF
14. ICU Discharge CRF
15. Day 28 CRF
16. Hospital Discharge CRF
17. Adverse Event CRF
18. 60-day Follow-up CRF
19. 90-day Follow-up CRF
20. Patient Disposition CRF
Screening Worksheet

1 Name of screener: _____________

2 Date/Time of Initial Screen:
   Date: _______________   Time (0-2400): ____________

3 Is patient 18-80 years old and intubated on Mechanical Ventilation  □ Yes  □ No
   a. If Yes continue screening
   b. If No do not screen

4 Is patient intubated (for <7 days) or trached and ventilated for <7 days?  □ Yes  □ No
   a. If Yes continue screening
   b. If No do not screen

5 If subject meets any of the following exclusion criteria, they are excluded. Complete Screening Form and indicate the relevant exclusion criteria:
   □ Missed ARDS window (>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
   □ Previously randomized in CHILL study
Berlin Criteria checklist (once checked yes, check N/A for subsequent data entry)

6 ARDS risk factor(s) met within 7 days of acute respiratory failure? □ Yes □ No

<table>
<thead>
<tr>
<th>Specify risk factor (Check all that apply)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Pneumonia/flu</td>
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<td></td>
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</tr>
<tr>
<td>□ Other sepsis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>□ Aspiration</td>
<td></td>
<td></td>
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<tr>
<td>□ Trauma</td>
<td></td>
<td></td>
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<tr>
<td>□ Transfusions</td>
<td></td>
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<tr>
<td>□ Pancreatitis</td>
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<td>□ Inhalation</td>
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<td>□ Drug Rxn</td>
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<tr>
<td>7 Date/time</td>
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</tr>
<tr>
<td>8 Bilateral infiltrates</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>□ Yes □ No</td>
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<tr>
<td>9 Not fully cardiogenic</td>
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<td></td>
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<tr>
<td>□ Yes □ No</td>
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<tr>
<td>□ N/A</td>
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<tr>
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<td>10 PEEP ≥5</td>
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</tr>
<tr>
<td>□ Yes □ No</td>
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<tr>
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<tr>
<td>□ Yes □ No</td>
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<tr>
<td>11 P/F &lt;300</td>
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<tr>
<td>□ N/A</td>
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<tr>
<td>□ Yes □ No</td>
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<tr>
<td>□ N/A</td>
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<tr>
<td>12 P/F &lt;200</td>
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<tr>
<td>□ Yes □ No</td>
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<tr>
<td>□ N/A</td>
<td></td>
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<td></td>
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<tr>
<td>□ Yes □ No</td>
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<tr>
<td>□ N/A</td>
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<tr>
<td>Date/time</td>
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<td></td>
</tr>
<tr>
<td>Bilateral infiltrates</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Not fully cardiogenic</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PEEP ≥5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P/F &lt;300</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>P/F &lt;200</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Met Berlin criteria for moderate to severe ARDS <48 hrs (refer to checklist) and P/F<200?

- Yes □ No □
  a. If criteria are NOT met continue to monitor patient until criteria met or patient meets one an exclusion criteria (frequency of re-evaluation depends on patient’s course) using table below
  b. If Berlin criteria are met and patient does not meet any exclusion criteria, complete Screening form and enroll.
Screening

1. Form Completed by ______________________

2. Date/Time of Initial Screen:   

3. Patient Location:  

4. Gender:  

5. Date of Birth:   

6. Ethnicity:  

7. Race: Asian:  

8. Was the patient offered enrollment?  

If NO indicate reason(s) below (answer Yes or No for all)  
- Missed ARDS window (>48hrs)  
- Missed NMB window: (>12 hrs)  
- Missed mechanical ventilation window (>7 days)  
- Refractory hypotension (> 0.2 mcg/kg/min of norepinephrine or equivalent dose for minimum of 6 h)  
- Core temperature <35.5°C while not receiving CRRT  
- No Legally authorized representative available  
- Significant, active bleeding (>2u blood products and/or surgical/IR intervention)  
- Platelets <10K/mm³ (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  
- On home O₂  
- On BIPAP (except for OSA)  
- Prior lung transplantation  
- BMI >45 kg/m²  
- Known NYHA class IV heart disease  
- Acute Coronary Syndrome past 30 days (MI, unstable angina)  
- Cardiac arrest within 30 days of enrollment  
- Previously randomized in CHILL study  

9. If offered enrollment did patient (LAR) consent?  

If Yes, proceed to Enrollment form.
ENROLLMENT

1. Date/time of form completion:

2. Form completed by: _______________________

3. Date/time of signed consent:

4. Epic note placed: □Yes □No.

5. Date/time all criteria for moderate/severe ARDS first met:

6. Date/time of first qualifying □CXR or □chest CT:

7. Number of quadrants with opacities: □2 □3 □4

8. Date/Time patient began continuous mechanical ventilation (<24 hour interruption)

9. Type of Airway: □Endotracheal tube □Tracheostomy

10. If tracheostomy, was tracheostomy placed within the previous 30 days? □Yes □No

11. If intubated Date/time of current intubation:

12. Qualifying P/F ratio: ______

13. Date/Time of Qualifying P/F ratio:
Clinical Research Enrollment note:

Patient name: _______________________    MRN#:____________________________

With informed consent, this patient was enrolled in the CHILL (Pilot RCT of Therapeutic Hypothermia in ARDS Patients Receiving Neuromuscular Blockade) study IRB #78506. I reviewed the records and determined that this patient meets all the inclusion criteria and the no exclusion for enrollment were identified, as documented on the Eligibility Checklist.

The patient or surrogate providing consent for this study expressed an understanding of the study and was provided an opportunity to ask questions regarding the study. Questions, if any have been answered. The signed consent was obtained before the start of any study procedures. The principal investigator, Dr. Hasday (8-8141). The Research Manager can be reached at 8-1473. A copy of the consent form, and HIPAA forms were given to the patient or surrogate and placed in the chart. All the records will be kept under key locked cabinets.

Signature _______________________________  Date: __________  Time: __________
RANDOMIZATION WORKSHEET

1. Date/time of enrollment: Date: _________ Time (0-2400):__________

2. Form completed by: ____________________________

3. Date/time all criteria for moderate/severe ARDS first met: Date: ________ Time:_______

4. Date/Time patient began continuous mechanical ventilation (<24 hour interruption)
   Date: ________ Time:__________

5. Date/Time NMB started? □ Yes (Date: _______ Time:______) □ No

6. Date/time that randomization window closes: Date:__________ Time:__________
   (7 days after intubation/ventilation, 48 hours after ARDS criteria met, or 12 hours after NMB started whichever occurs first)

7. Use following checklist to monitor for randomization

<table>
<thead>
<tr>
<th>Evaluation number</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date/time</td>
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</tr>
<tr>
<td>NMB</td>
<td></td>
<td></td>
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<tr>
<td>Started &lt;12hrs</td>
<td>□</td>
<td>No</td>
<td>□</td>
</tr>
<tr>
<td>Order placed</td>
<td>□</td>
<td>No</td>
<td>□</td>
</tr>
<tr>
<td>P/F &lt;150</td>
<td>□</td>
<td>No</td>
<td>□</td>
</tr>
<tr>
<td>Met ARDS criteria</td>
<td>□</td>
<td>No</td>
<td>□</td>
</tr>
<tr>
<td>&lt;48hr</td>
<td>□</td>
<td>No</td>
<td>□</td>
</tr>
<tr>
<td>Intubated/ventilated &lt;7 days</td>
<td>□</td>
<td>No</td>
<td>□</td>
</tr>
</tbody>
</table>

8. Randomization criteria met: □ Yes (Date: _______ Time:______) □ No

   If Yes, proceed to Randomization form.

   If No,

9. Indicate reason(s) (Check all that apply): □ Patient died   □ P/F ≥ 150 within inclusion window
   □ NMB not started or ordered within inclusion window □ Withdrawn by LAR or ICU provider
RANDOMIZATION

1 Form Completed by ____________________________

Note: In order to randomize, patient must meet randomization criteria, have accessible baseline data and have had the baseline research blood sample drawn.

2 Randomized: ☐ Yes ☐ No

If Yes,

3 Randomization Date/Time:

4 Is patient currently being proned? ☐ Yes ☐ No

5 Treatment assignment: ☐ Hypothermia arm ☐ Usual Temperature Management arm

6 Assignment made by: ____________________________

7 If patient was not randomized, indicate reason(s) below (Check Yes or No for all potential reasons below):

- Missed ARDS window (>48hrs) ☐ Yes ☐ No
- Missed NMB window: (>12 hrs) ☐ Yes ☐ No
- Missed mechanical ventilation window (>7 days) ☐ Yes ☐ No
- Refractory hypotension
  - (> 0.2 mcg/kg/min norepinephrine or equivalent dose for ≥6 h) ☐ Yes ☐ No
- Significant, active bleeding (>2u blood products or surgical/IR intervention) ☐ Yes ☐ No
- Consent withdrawn ☐ Yes ☐ No
- Primary provider withdrew approval ☐ Yes ☐ No
- Status change to Do Not Resuscitate ☐ Yes ☐ No
- Acute Coronary Syndrome (STEMI, NSTEMI type I, unstable angina) ☐ Yes ☐ No
- Interval moribund status (not expected to survive at least 72 hours) ☐ Yes ☐ No
- Unlikely to remain intubated for at least 48 hours) ☐ Yes ☐ No

If patient randomized to hypothermia arm, have a member of the MICU provider team enter the UMMC MED-CC Hypothermia Following Arrest Supplemental order set in Epic with the following modifications:

- 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, cistiracrium.
- Under Chemistry, select Comprehensive Metabolic Panel
- Modify Hyper/Hypothermia order by changing stop date from 24h to 48 h. Change Comments: “Lower patient’s temperature to 34 – 35C as quickly as possible per protocol. Maintain hypothermia 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 are underlined and bolded.)
Contact Information:

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:  
BASELINE DATA

1. Form Completed by ____________________________

2. Hospital admission date: __________/________/________

3. Hospital admission type: □ Medical □ Surgical □ Trauma

4. ICU admission Date/Time: __________/________/________

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 Pack-years _____
   □ Former smoker Peak Pack-years _____
   Quit date __________/________/________

8. Has the patient had surgery within the last week? □ Yes □ No Date: __________/________/________

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 □ Vascular □ 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  □ I.V.  □ Peripheral

11 Systolic BP:  Lowest [ ] mm Hg  Highest [ ] mm Hg  Single [ ]
Mean arterial pressure:  Lowest [ ] mm Hg  Highest [ ] mm Hg  Single [ ]
Heart rate:  Lowest [ ] beats/min  Highest [ ] beats/min  Single [ ]
Respiratory rate:  Lowest [ ] breaths/min  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 Laboratory data (if only one value, record in “Lowest” field and click “Single” box; if no data, click “None” box):

**CBC values:**
- WBC:  Lowest [ ] x1000/mm³  Highest [ ] x1000/mm³  Single [ ]  None [ ]
- Hgb:  Lowest [ ] g/dL  Highest [ ] g/dL  Single [ ]  None [ ]
- Hct:  Lowest [ ] %  Highest [ ] %  Single [ ]  None [ ]
- Platelets:  Lowest [ ] x1000/mm³  Single [ ]  None [ ]

**Serum Levels:**
- Sodium:  Lowest [ ] mEq/L  Highest [ ] mEq/L  Single [ ]  None [ ]
- Potassium:  Lowest [ ] mEq/L  Highest [ ] mEq/L  Single [ ]  None [ ]
- Bicarbonate:  Lowest [ ] mEq/dL  Highest [ ] mEq/dL  Single [ ]  None [ ]
- BUN:  Lowest [ ] mg/dL  Highest [ ] mg/dL  Single [ ]  None [ ]
- Creatinine:  Lowest [ ] mg/dL  Highest [ ] mg/dL  Single [ ]  None [ ]
- Glucose:  Lowest [ ] mg/dL  Highest [ ] mg/dL  Single [ ]  None [ ]
- Magnesium:  Lowest [ ] mmol/L  Highest [ ] mmol/L  Single [ ]  None [ ]
- Phosphate:  Lowest [ ] mg/dL  Highest [ ] mg/dL  Single [ ]  None [ ]
- Albumin:  Lowest [ ] g/dL  Highest [ ] g/dL  Single [ ]  None [ ]
- Bilirubin:  Lowest [ ] mg/dL  Highest [ ] mg/dL  Single [ ]  None [ ]

Highest AST [ ] U/L  None [ ]  Highest ALT [ ] U/L  None [ ]
Respiratory Parameters:

For the 24 hours preceding randomization, record the lowest measured post-intubation SpO₂ (with an adequate waveform) date and time of measurement, and the corresponding Mean Airway Pressure, measured PEEP, and FiO₂. And the post-intubation ABG with the lowest PaO₂, the date and time that the ABG sample was collected and the corresponding Mean Airway Pressure, FiO₂ and measured PEEP.

SpO₂:

<table>
<thead>
<tr>
<th>Lowest SpO₂:</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date/Time of SpO₂ measurement:</td>
<td></td>
</tr>
<tr>
<td>Corresponding Mean Airway Pressure:</td>
<td>cm H₂O</td>
</tr>
<tr>
<td>Corresponding Measured PEEP:</td>
<td>cm H₂O</td>
</tr>
<tr>
<td>Corresponding FiO₂:</td>
<td>%</td>
</tr>
</tbody>
</table>

ABG:

<table>
<thead>
<tr>
<th>Lowest PaO₂:</th>
<th>mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH:</td>
<td></td>
</tr>
<tr>
<td>Date/Time of ABG collection:</td>
<td></td>
</tr>
<tr>
<td>Corresponding Mean Airway Pressure:</td>
<td>cm H₂O</td>
</tr>
<tr>
<td>Corresponding Measured PEEP:</td>
<td>cm H₂O</td>
</tr>
<tr>
<td>Corresponding FiO₂:</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Ventilator Parameters (record most recent values prior to randomization)

16 Date/Time of recorded settings:

17 Ventilator/ Mode

☐ DRAEGER
☐ VC-CMV ☐ SPN-CPAP/PS ☐ VC-AC ☐ BiVent
☐ PC-CMV ☐ SPN-CPAP/VS ☐ PC-AC ☐ PS
☐ PC-AC ☐ SPN-PPS ☐ PRVC ☐ VS
☐ PC-SIMV ☐ VC-MMV ☐ VC-SIMV ☐ CPAP
☐ PC-BIPAP ☐ SPN-CPAP ☐ PC-SIMV ☐ NIV
☐ PC-APRV ☐ PRVC-SIMV
☐ PC-HFO
☐ PC-MMV
☐ Other

For volume targeted modes: Set tidal volume: _______ ml
For pressure control/dual mode: Inspiratory Time: _______ sec; Pressure _______ cm H₂O
Set rate: _______ breaths/min PEEP cm H₂O
If APRV/BiVENT: P₁/high _______ cm H₂O P₂/PEEP _______ cm H₂O T₁/high _______ sec
T₂/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 H₂O (at PEEP and FiO₂ recorded above)
Peak Inspiratory pressure: _______ cm H₂O Mean airway pressure: _______ cm H₂O
I:E ratio _______ .

23 ARDSnet Guideline Checklist
Is tidal volume 5-7 ml/kg?: ☐ Yes ☐ No
Is plateau pressure* ≤ 30 cm H₂O?: ☐ Yes ☐ No
Is SpO₂ between 88 and 95%? ☐ Yes ☐ No
Is RR < 35 BPM? ☐ Yes ☐ No
Is I:E ratio between 1 and 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:

24 Post-change measurements:
Tidal Volume: _______ ml Plateau Pressure*: _______ cm H₂O PEEP: _______ cm H₂O

*Plateau pressure or equivalent (Peak Inspiratory Pressure on PS/PC, P₁/high on APRV/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 H₂O OR [__] CVP not available Temperature [__] °C

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: [__] [__] [__] [__] [__] [__]

□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 Date/Time NMB was started: [__] [__] [__] [__] [__] [__]

31 If proning protocol initiated, Date/Time proning protocol initiated:

32 If in hypothermia group, Date/Time cooling was initiated:

33 Cooling method(s) used:

□Blanketrol cooling blanket □Artic Sun □Ice packs □Intravenous □Gastric

34 Research blood sample collected:

□ Yes □No

35 Blood collected: [__] [__] [__] [__] [__] [__] Processed: [__] [__] [__] [__] [__] [__]

36 Number 0.5 ml aliquots: □1 □2 □3 □4 □5 □6 □7 □8 □9 □10

37 Date/Time placed in -80°C freezer: [__] [__] [__] [__] [__]

38 Location in freezer: ____________ Temperature reading on freezer: [__] °C
DAILY DATA – Day 01
(to be obtained between 0600 and 1000 the day after randomization)

1 Form Completed by ____________________

2 Vital status □ Alive □ Dead

3 If Dead Date/Time of death:

4 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

5 Still receiving NMB? □ Yes □ No  If “Yes” skip to question 8

   Date/Time NMB discontinued:

6 Reason for discontinuation: □ Refractory bradycardia  □ Possible drug reaction
   □ Decision of ICU provider  □ Decision of family

7 Date/Time: neuromuscular function (4 twitches/TOF) returned:

   or □ Did not return

8 Is patient in hypothermia group? □ Yes □ No  If “No” skip to question 11

9 Minutes to reach 35°C from randomization: _______ from initiation of cooling: _______

10 Still being cooled? □ Yes □ No  If “Yes” skip to question 12

   If No, when was cooling stopped?

   Reason for discontinuation: □ Refractory bradycardia with hypotension  □ Hemorrhage
   □ Single □ CVP arrhythmia    □ Decision of ICU provider  □ Decision of family

Skip to question 12.

11 If in the Control arm, received therapeutic hypothermia in last 24 hrs? □ Yes □ No □ N/A

12 Still intubated or receiving Assisted Breathing? □ Yes □ No □ N/A

   If “No,” when was patient extubated or UAB for ≥48 hours?

13 Was RRT started since randomization? □ Yes □ No □ N/A

14 If RRT had been previously initiated has it stopped since randomization? □ Yes □ No □ N/A

15 Since randomization did the patient have any of the following:

   □ Bradycardia (with mean arterial pressure < 65 mm Hg or needingpressors) □ Yes □ No
   □ Significant Bleeding (Required IR, Surgery or >3u pRBCs) □ Yes □ No
   □ Diagnosis of new pneumonia □ Yes □ No

16 Vital signs since randomization

   Systolic BP: Lowest: _______ Highest: _______ mm Hg  Single □
   Diastolic BP: Lowest: _______ Highest: _______ mm Hg  Single □
   CVP: Lowest: _______ Highest: _______ cm H₂O  CVP not available □ Single □
   Mean arterial pressure: Lowest: _______ Highest: _______ mm Hg  Single □
For each 2 hr block from time of randomization until 0800 of DAY AFTER randomization record highest and lowest temperature and lowest SpO₂ and corresponding FiO₂ and Mean Airway Pressure. If only single temperature measurement for block, check “Single value” box. If no SpO₂ measured for block, check the “None” box.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Temp (°C)</th>
<th>Date/Time (If single value check box)</th>
<th>Site of Temp measurement</th>
<th>Low SpO₂ (pulse Ox) (%)</th>
<th>FiO₂ (%)</th>
<th>Mean airway pressure (cm H₂O)</th>
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**DAY 1 AFTER RANDOMIZATION**

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</table>
Since randomization did patient receive?

18 Corticosteroid: ☐ Yes ☐ No If yes, total daily dose (prednisone equivalent): □ □ □ □ mg

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

19 Inhaled vasodilator: ☐ Yes ☐ No If "Yes": indicate agent(s) used and total hrs administered

☐ Epoprostenol ☐ Nitric Oxide Total hours administered: □ □ □ □

20 Vasopressor support since randomization ☐ Yes ☐ No If No proceed to question 21. (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: □ □ □ □ □ □

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

CBC values:

WBC: □ □ □ □ Single □ □ □ □ x1000/mm³ Lowest: □ □ □ □ Highest: □ □ □ □ None □

x1000/mm³ Single □ □ □ □ Hgb: □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ g/dL Single □ None □

Hct: □ □ □ □ % Single □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ None □

% Platelets: □ □ □ □ Lowest: □ □ □ □ x1000/mm³ None □

Serum Levels:

Potassium: □ □ □ □ mEq/L Single □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ None □

Bicarbonate: □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ mEq/dL Single □ None □

BUN: □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ mg/dL Single □ None □

Creatinine: □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ mg/dL Single □ None □

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

Magnesium:

mmol/L Single □ □ □ □ None □ Phosphate

mg/dL Single □ □ □ □ None □

Albumin: Single □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ None □

g/dL Single □ □ □ □ Lowest: □ □ □ □ Highest: □ □ □ □ None □

Bilirubin: Lowest: □ □ □ □ Highest: mg/dL Single □ None □

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

22 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:
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<th>Lowest Glucose (mg/dL)</th>
<th>Date</th>
<th>Time</th>
<th>Highest Glucose (mg/dL)</th>
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<th>Time</th>
<th>Single value</th>
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<td><strong>DAY 1 AFTER RANDOMIZATION</strong></td>
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23 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
☐ Other ______________

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

24 Extubated: ☐ Yes ☐ No  If Yes, Date/Time of extubation: ___________ ___________ ___________ ___________ ___________ ___________ ___________ ___________

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

25 Measured Tidal Volumes: Lowest: ___________ ml Highest: ___________ ml

26 Estimated hours patient ventilated with tidal volume > 7 ml/kg ___________ hrs

27 Applied PEEP: Lowest: ___________ cm H₂O Highest: ___________ cm H₂O

28 Mean airway pressure: Lowest: ___________ cm H₂O Highest: ___________ cm H₂O

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)

29 Plateau Pressure: ___________ cm H₂O and associated PEEP: ___________ cm H₂O.

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)

30 PaO₂/FiO₂: Lowest: ___________ mm Hg/___________ %Highest: ___________ mm Hg/___________ %mm Hg

Single Value: ☐ None: ☐

Fluid Management:

31 Total Intake since randomization: ___________ mL

32 Total Output since randomization (include dialysis/CRRT): ___________ mL
33 Plasma sample collected: □ Yes □ No

34 Blood collected:  

35 Number 0.5 ml aliquots: □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

36 Date/Time placed in -80°C freezer:

37 Location in freezer: _____________ Temperature reading on freezer: -____ °C
DAILY DATA – Day 02
(to be obtained between 0600 and 1000 day 2 after randomization)

1 Form Completed by __________________________

2 Vital status □ Alive □ Dead

3 If Dead Date/Time of death:

4 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

5 Still receiving NMB? □ Yes □ No

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

6 Reason for discontinuation: □ Refractory bradycardia  □ Possible drug reaction
□ Decision of ICU provider  □ Decision of family

7 Date/Time: neuromuscular function (4 twitches/TOF) returned:

or □ Did not return

8 Is patient in hypothermia group? □ Yes □ No  If “No” skip to question 10

9 Still being cooled? □ Yes □ No  If “Yes” skip to question 11

If No, when was cooling stopped?

Reason for discontinuation: □ Refractory bradycardia with hypotension  □ Hemorrhage
□ Intractable ventricular arrhythmia □ Decision of ICU provider □ Decision of family

Skip to question 11.

10 If in the Control arm, received therapeutic hypothermia in last 24 hrs? □ Yes □ No □ N/A

11 Still intubated or receiving Assisted Breathing? □ Yes □ No □ N/A

If No, when was patient extubated or UAB for ≤48 hours?

12 Was RRT started in last 24 hrs? □ Yes □ No □ N/A

13 If RRT had been previously initiated has it stopped since randomization? □ Yes □ No □ N/A

14 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

15 Vital signs in last 24 hrs

Systolic BP: Lowest: ____ Highest: _____ mm Hg  Single □

Diastolic BP: Lowest: _____ Highest: _____ mm Hg  Single □

CVP: Lowest: _____ Highest: _____ cm H₂O  CVP not available □ Single □

Mean arterial pressure: Lowest: _____ Highest: _____ mm Hg  Single □
For each 2 hr block for the last 24 hrs record highest and lowest temperature and lowest SpO₂ and corresponding FiO₂ and Mean Airway Pressure. If only single temperature measurement for block, check “Single value” box. If no SpO₂ measured for block, check the “None” box.

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<td>2201-2400 High:</td>
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<td>□ Esophageal □ Urinary</td>
<td>□ None</td>
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<tr>
<td>Low:</td>
<td></td>
<td>□ Peripheral □ IV</td>
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<td><strong>DAY 2 AFTER RANDOMIZATION</strong></td>
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<tr>
<td>0001-0200 High:</td>
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<td>□ None</td>
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<tr>
<td>Low:</td>
<td></td>
<td>□ Peripheral □ IV</td>
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<td>□ Esophageal □ Urinary</td>
<td>□ None</td>
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<tr>
<td>Low:</td>
<td></td>
<td>□ Peripheral □ IV</td>
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<tr>
<td>0401-0600 High:</td>
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<td>□ Esophageal □ Urinary</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low:</td>
<td></td>
<td>□ Peripheral □ IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0601-0800 High:</td>
<td></td>
<td>□ Esophageal □ Urinary</td>
<td>□ None</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low:</td>
<td></td>
<td>□ Peripheral □ IV</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

In last 24 hours did patient receive?

Corticosteroid: □ Yes □ No If yes, total daily dose (prednisone equivalent): □ □ □ mg

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

Inhaled vasodilator: □ Yes □ No If "Yes": indicate agent(s) used and total hrs administered

□ Epoprostenol □ Nitric Oxide Total hours administered: □ □
19 Vasopressor support in last 24 hrs □ Yes □ No  If No proceed to question 20. (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: □

20 Laboratory data (if only one value, record in “Lowest” field and click “Single” box; if no data, click “None” box):

**CBC values:**
- WBC: □ □ □ □ Single □ □ □ □ None □
  - x1000/mm³
- Hgb: Lowest: □ □ □ □ Single □ □ □ □ None □
  - g/dL
- Hct: □ □ □ □ Single □ □ □ □ None □
  - %
- Platelets: Lowest: □ □ □ □ x1000/mm³
  - None □

**Serum Levels:**
- Potassium: □ □ □ □ Single □ □ □ □ None □
  - mEq/L
- Bicarbonate: Lowest: □ □ □ □ Single □ □ □ □ None □
  - mEq/dL
- BUN: Lowest: □ □ □ □ Single □ □ □ □ None □
  - mg/dL
- Creatinine: Lowest: □ □ □ □ Single □ □ □ □ None □
  - mg/dL
- Glucose: □ □ □ □ Single □ □ □ □ None □
  - mg/dL
- Magnesium: □ □ □ □ Single □ □ □ □ None □
  - mmol/L
- Phosphate: □ □ □ □ Single □ □ □ □ None □
  - mg/dL
- Albumin: □ □ □ □ Single □ □ □ □ None □
  - g/dL
- Bilirubin: Lowest: □ □ □ □ Single □ □ □ □ None □
  - mg/dL
- AST: □ □ □ □ Single □ □ □ □ None □
  - U/L
- ALT: □ □ □ □ Single □ □ □ □ None □
  - U/L

21 Highest/Lowest finger stick glucose every 6 hrs for last 24 hrs (if only single value, enter in “Lowest” field and check “Single value” box; If no data, check “None” box:}

---

3
If patient was extubated/UAB prior to Study Day 2, go to question 29.

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

☐ DRAEGER

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

23 Extubated:  ☐ Yes  ☐ No  If Yes, Date/Time of extubation: __________

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

24 Measured Tidal Volumes:  Lowest: ______ ml  Highest: ______ ml

25 Estimated hours patient ventilated with tidal volume > 7 ml/kg  ______ hrs

26 Applied PEEP:  Lowest: ______ cm H₂O  Highest: ______ cm H₂O

27 Mean airway pressure:  Lowest: ______ cm H₂O  Highest: ______ cm H₂O

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)

28 Plateau Pressure: ______ cm H₂O and associated PEEP: ______ cm H₂O.

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)

29 PaO₂/FiO₂:  Lowest: ______ mm Hg  %Highest: ______ mm Hg

Single Value:  ☐  None:  ☐
Fluid Management:

30 Total Intake since randomization: [______] mL

31 Total Output since randomization (include dialysis/CRRT): [______] mL

32 Plasma sample collected: [ ] Yes [ ] No

33 Blood collected: [______] [______] [______] [______] Processed: [______] [______] [______] [______]

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

35 Date/Time placed in -80°C freezer: [______] [______] [______] [______] [______] [______] [______]

36 Location in freezer: ________________ Temperature reading on freezer: ______°C
DAILY DATA – Day 03
(to be obtained between 0600 and 1000 day 3 after randomization)

1 Form Completed by ____________________________

2 Vital status  □ Alive  □ Dead

3 If Dead Date/Time of death:

4 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

5 Still receiving NMB?  □ Yes  □ No
   If No and discontinued in last 24 hrs, answer following questions:
   If No Date/Time discontinued:

6 Reason for discontinuation:  □ Refractory bradycardia  □ Possible drug reaction
   □ Decision of ICU provider  □ Decision of family

7 Date/Time: neuromuscular function (4 twitches/TOF) returned:
   or  □ Did not return

8 Is patient in hypothermia group?  □ Yes  □ No  If “No” skip to question 10

9 Still being cooled?  □ Yes  □ No  If “Yes” skip to question 11
   If No, when was cooling stopped?

Reason for discontinuation:  □ Refractory bradycardia with hypotension  □ Hemorrhage
   □ Intractable ventricular arrhythmia  □ Decision of ICU provider  □ Decision of family

Skip to question 11.

10 If in the Control arm, received therapeutic hypothermia in last 24 hrs?  □ Yes  □ No  □ N/A

11 Still intubated or receiving Assisted Breathing?  □ Yes  □ No  □ N/A
   If No, when was patient extubated or UAB for ≤48 hours?

12 Was RRT started in last 24 hrs?  □ Yes  □ No  □ N/A

13 If RRT had been previously initiated has it stopped since randomization?  □ Yes  □ No  □ N/A

14 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

15 Vital signs in last 24 hrs

   Systolic BP: Lowest:  □□□□□□  Highest:  □□□□□□ mm Hg  Single □
   Diastolic BP: Lowest:  □□□□□□  Highest:  □□□□□□ mm Hg  Single □
   CVP: Lowest:  □□□□□□  Highest:  □□□□□□ cm H₂O  CVP not available □ Single □
   Mean arterial pressure: Lowest:  □□□□□□  Highest:  □□□□□□ mm Hg  Single □
For each 2 hr block for the last 24 hrs record highest and lowest temperature and lowest \( \text{SpO}_2 \) and corresponding \( \text{FiO}_2 \) and Mean Airway Pressure. If only single temperature measurement for block, check “Single value” box. If no \( \text{SpO}_2 \) measured for block, check the “None” box.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Temp (°C)</th>
<th>Date/Time (If single value check box)</th>
<th>Site of Temp measurement</th>
<th>Low ( \text{SpO}_2 ) (pulse Ox) (%)</th>
<th>( \text{FiO}_2 ) (%)</th>
<th>Mean airway pressure (cm H(_2)O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY 2 AFTER RANDOMIZATION</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0801-1000</td>
<td>High:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
<td></td>
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<tr>
<td>0801-1000</td>
<td>Low:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<td></td>
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<tr>
<td>1001-1200</td>
<td>High:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<td></td>
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<tr>
<td>1001-1200</td>
<td>Low:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1201-1400</td>
<td>High:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<td></td>
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<tr>
<td>1201-1400</td>
<td>Low:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<td></td>
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<tr>
<td>1401-1600</td>
<td>High:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
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<tr>
<td>1401-1600</td>
<td>Low:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<tr>
<td>1601-1800</td>
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<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<tr>
<td>1601-1800</td>
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<td>☐ Peripheral ☐ IV</td>
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<td>☐ Peripheral ☐ IV</td>
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<td>☐ Peripheral ☐ IV</td>
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<tr>
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<td>☐ Peripheral ☐ IV</td>
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<td>2201-2400</td>
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<td>☐ Peripheral ☐ IV</td>
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<td>DAY 3 AFTER RANDOMIZATION</td>
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<td>0001-0200</td>
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<td>☐ Peripheral ☐ IV</td>
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<tr>
<td>0001-0200</td>
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<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<tr>
<td>0201-0400</td>
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<td>☐ Peripheral ☐ IV</td>
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<tr>
<td>0201-0400</td>
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<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<tr>
<td>0401-0600</td>
<td>High:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<tr>
<td>0401-0600</td>
<td>Low:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<tr>
<td>0601-0800</td>
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<td>☐ Peripheral ☐ IV</td>
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<tr>
<td>0601-0800</td>
<td>Low:</td>
<td>☐ Esophageal ☐ Urinary</td>
<td>☐ Peripheral ☐ IV</td>
<td>None ☐</td>
<td></td>
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</tr>
</tbody>
</table>

In last 24 hours did patient receive?
17**Corticosteroid:** ☐ Yes ☐ No If yes, total daily dose (prednisone equivalent): ☐ ☐ mg
1 mg prednisone/methylprednisolone = 4 mg hydrocortisone; 1 mg dexamethasone = 25 mg hydrocortisone

18**Inhaled vasodilator:** ☐ Yes ☐ No If “Yes”: indicate agent(s) used and total hrs administered
☐ Epoprostenol ☐ Nitric Oxide Total hours administered: ☐ ☐
19. **Vasopressor support in last 24 hrs** □ Yes □ No  
If No proceed to question 20.  
(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: □

20. **Laboratory data** (if only one value, record in “Lowest” field and click “Single” box; if no data, click “None” box):  
**CBC values:**  
- WBC: □, □  
  x1000/mm³ Single □, □  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Hgb: Lowest: □, □  
  Highest: □, □ g/dL  
  Single □  
  None □  
- Hct: Lowest: □, □  
  Highest: □, □ %  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Platelets: Lowest: □□□□ x1000/mm³  
  Highest: □□□□  
  None □

**Serum Levels:**  
- Potassium: □, □  
  mEq/L Single □, □  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Bicarbonate: Lowest: □, □  
  Highest: □, □ mEq/dL  
  Single □  
  None □  
- BUN: Lowest: □, □  
  Highest: □, □ mg/dL  
  Single □  
  None □  
- Creatinine: Lowest: □, □  
  Highest: □, □ mg/dL  
  Single □  
  None □  
- Glucose: □□□□ mg/dL  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Magnesium: □, □  
  mmol/L Single □, □  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Phosphate: □, □  
  Lowest: □, □  
  Highest: □, □  
  None □  
- mg/dL Single □, □  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Albumin: □□□□ g/dL  
  Lowest: □, □  
  Highest: □, □  
  None □  
- Bilirubin: Lowest: □, □ mg/dL  
  Highest: □, □  
  Single □  
  None □  
- Highest AST: □□□□ U/L  
  Lowest: □, □  
  Highest ALT: □□□□ U/L  
  None □

21. **Highest/Lowest finger stick glucose every 6 hrs for last 24 hrs** (if only single value, enter in “Lowest” field and check “Single value” box; if no data, check “None” box:  

---

1. **SITE ID** | **PATIENT ID** | **LETTER CODE**
---|---|---
---

CHILL-pilot RCT  Day 03 Data (Ver. 1.1)
If patient was extubated/UAB prior to Study Day 3, go to question 29.

25 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

23 Extubated:  ☐ Yes  ☐ No  If Yes, Date/Time of extubation:

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

24 Measured Tidal Volumes:  Lowest:  ml  Highest:  ml

25 Estimated hours patient ventilated with tidal volume > 7 ml/kg  hrs

26 Applied PEEP:  Lowest:  cm H₂O  Highest:  cm H₂O

27 Mean airway pressure:  Lowest:  cm H₂O  Highest:  cm H₂O

Lung Physiology Parameters (recorded 0600 to 1000 day 3 post-randomization; If no data available, check “No values” box. If patient not intubated, check “Not intubated” box)

28 Plateau Pressure:  cm H₂O and associated PEEP:  cm H₂O.

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)

29 PaO₂/FiO₂:  Lowest:  mm Hg  %Highest:  mm Hg  %mm Hg

Single Value:  ☐  None:  ☐
Fluid Management:

30 Total Intake since randomization: [___] mL

31 Total Output since randomization (include dialysis/CRRT): [___] mL

32 Plasma sample collected: □ Yes □ No

33 Blood collected: [___] Processed: [___]

34 Number 0.5 ml aliquots: □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

35 Date/Time placed in -80°C freezer: [___] Temperature reading on freezer: _____ °C

36 Location in freezer: ____________
DAILY DATA – Day 04
(to be obtained between 0600 and 1000 day 4 after randomization)

1 Form Completed by ________________________

2 Vital status □ Alive □ Dead

3 If Dead Date/Time of death:

4 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

5 Still receiving NMB? □ Yes □ No
If No and discontinued in last 24 hrs, answer following questions:
If No Date/Time discontinued:

6 Reason for discontinuation: □ Refractory bradycardia □ Possible drug reaction
□ Decision of ICU provider □ Decision of family

7 Date/Time: neuromuscular function (4 twitches/TOF) returned:
or □ Did not return

8 Is patient in hypothermia group? □ Yes □ No  If “No” skip to question 10

9 Did the patient complete 48 hrs of hypothermia? □ Yes □ No  If “Yes” skip to question 11
If No, when was cooling stopped?

Reason for discontinuation: □ Refractory bradycardia with hypotension □ Hemorrhage
□ Intractable ventricular arrhythmia □ Decision of ICU provider □ Decision of family

Skip to question 11.

10 If in the Control arm, received therapeutic hypothermia in last 24 hrs? □ Yes □ No □ N/A

11 Still intubated or receiving Assisted Breathing? □ Yes □ No □ N/A
If No, when was patient extubated or UAB for ≤48 hours?

12 Was RRT started in last 24 hrs? □ Yes □ No □ N/A

13 If RRT had been previously initiated has it stopped since randomization? □ Yes □ No □ N/A

14 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

15 Vital signs in last 24 hrs
Systolic BP: Lowest: __________ Highest: __________ mm Hg  Single □
Diastolic BP: Lowest: __________ Highest: __________ mm Hg  Single □
CVP: Lowest: __________ Highest: __________ cm H₂O  CVP not available □ Single □
Mean arterial pressure: Lowest: __________ Highest: __________ mm Hg  Single □
For each 2 hr block for the last 24 hrs record highest and lowest temperature and lowest SpO₂ and corresponding FiO₂ and Mean Airway Pressure. If only single temperature measurement for block, check “Single value” box. If no SpO₂ measured for block, check the “None” box.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Temp (°C)</th>
<th>Date/Time (If single value check box ▼)</th>
<th>Site of Temp measurement</th>
<th>Low SpO₂ (pulse Ox) (%)</th>
<th>FiO₂ (%)</th>
<th>Mean airway pressure (cm H₂O)</th>
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<td>Low:</td>
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<td>□ Peripheral □ IV</td>
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</table>

In last 24 hours did patient receive?

**Corticosteroid:** □ Yes □ No If yes, total daily dose (prednisone equivalent): □□□ mg

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

**Inhaled vasodilator:** □ Yes □ No If "Yes": indicate agent(s) used and total hrs administered

□ Epoprostenol □ Nitric Oxide Total hours administered: □□
19. Vasopressor support in last 24 hrs [ ] Yes [ ] No If No proceed to question 20. (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
   - [ ] Vaspressin [ ] units/min
   - [ ] Phenylephrine [ ] µg/kg/min OR [ ] µg/min
   - [ ] Milrinone [ ] µg/kg/min OR [ ] µg/min
   Total hours receiving vasopressor support: [ ]

20. Laboratory data (if only one value, record in “Lowest” field and click “Single” box; if no data, click “None” box):
   **CBC values:**
   - WBC: [ ] Single [ ] Lower: [ ] Highest: [ ] None [ ]
   - x1000/mm³ [ ] None [ ]
   - Hgb: Lowest: [ ] Highest: [ ] g/dL [ ] Single [ ] None [ ]
   - Hct: None [ ]
   - % [ ] Single [ ] None [ ]
   - Platelets: Lowest: [ ] x1000/mm³ [ ] None [ ]
   **Serum Levels:**
   - Potassium: [ ] Single [ ] Lower: [ ] Highest: [ ] None [ ]
   - mEq/L [ ] None [ ]
   - Bicarbonate: Lowest: [ ] Highest: [ ] mEq/dL [ ] Single [ ] None [ ]
   - BUN: Lowest: [ ] Highest: [ ] mg/dL [ ] Single [ ] None [ ]
   - Creatinine: Lowest: [ ] Highest: [ ] mg/dL [ ] Single [ ] None [ ]
   - Glucose: [ ] Single [ ] None [ ]
   - mg/dL [ ] None [ ]
   - Magnesium: [ ] Single [ ] None [ ]
   - mmol/L [ ] None [ ]
   - Phosphate: [ ] Single [ ] None [ ]
   - mg/dL [ ] None [ ]
   - Albumin: [ ] Single [ ] None [ ]
   - g/dL [ ] None [ ]
   - Bilirubin: Lowest: [ ] Highest: [ ] mg/dL [ ] Single [ ] None [ ]
   - Highest AST: [ ] U/L None [ ] Highest ALT: [ ] U/L None [ ]

21. Highest/Lowest finger stick glucose every 6 hrs for last 24 hrs (if only single value, enter in “Lowest” field and check “Single value” box; If no data, check “None” box: [ ]
### Day 4 After Randomization

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<th>Date</th>
<th>Time</th>
<th>Highest Glucose</th>
<th>Date</th>
<th>Time</th>
<th>Single value</th>
<th>None</th>
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</table>

If patient was extubated/UAB prior to Study Day 4, go to question 29.

23 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
  - BiVent
  - PC-SIMV
  - VC-SIMV
  - SPN-PPS
  - PRVC
  - VS
  - PC-BIPAP
  - VC-MMV
  - SPN-CPAP
  - PC-APRV
  - PC-HFO
  - PC-MMV
  - Other ____________

23 Extubated: [ ] Yes [ ] No  
If Yes, Date/Time of extubation: ____________

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

24 Measured Tidal Volumes: Lowest: ____________ ml  
Highest: ____________ ml

25 Estimated hours patient ventilated with tidal volume > 7 ml/kg: ____________ hrs

26 Applied PEEP: Lowest: ____________ cm H₂O  
Highest: ____________ cm H₂O

27 Mean airway pressure: Lowest: ____________ cm H₂O  
Highest: ____________ cm H₂O

Lung Physiology Parameters (recorded 0600 to 1000 day 3 post-randomization; If no data available, check “No values” box. If patient not intubated, check “Not intubated” box)

28 Plateau Pressure: ____________ cm H₂O  
and associated PEEP: ____________ cm H₂O.

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)

29 PaO₂ /FiO₂: Lowest: ____________ mm Hg  
% Highest: ____________ mm Hg

Single Value: [ ] None: [ ]
**Fluid Management:**

30 Total Intake since randomization: [Blank] mL

31 Total Output since randomization (include dialysis/CRRT): [Blank] mL

32 **Plasma sample collected:** ☐ Yes ☐ No

33 Blood collected: [Blank] Processed: [Blank]

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

35 Date/Time placed in -80°C freezer: [Blank]

36 Location in freezer: ____________ Temperature reading on freezer: ______°C
DAILY DATA – Day 07
(to be obtained between 0600 and 1000 day 7 after randomization)

1. Form Completed by _______________________

2. Vital status  □ Alive □ Dead
   If Dead Date/Time of death:

3. 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. Still receiving NMB?  □ Yes  □ No
   If No and discontinued in last 24 hrs, answer following questions:
   If No Date/Time discontinued:

5. Reason for discontinuation:  □ Refractory bradycardia  □ Possible drug reaction
   □ Decision of ICU provider  □ Decision of family

6. Date/Time: neuromuscular function (4 twitches/TOF) returned:
   or  □ Did not return

7. Did patient receive therapeutic hypothermia in last 72 hours?  □ Yes  □ No

8. Still intubated or receiving Assisted Breathing?  □ Yes  □ No  □ N/A
   If No, when was patient extubated or UAB for ≤48 hours?

9. Was RRT started in last 24 hrs?  □ Yes  □ No  □ N/A

10. If RRT had been previously initiated has it stopped since randomization?  □ Yes  □ No  □ N/A

11. In the last 24 hrs did the patient have any of the following:
    Brady-cardia (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

12. Vital signs in last 24 hrs
    Systolic BP: Lowest: [ ] [ ]  Highest: [ ] [ ] mm Hg  single  □
    Diastolic BP: Lowest: [ ] [ ]  Highest: [ ] [ ] mm Hg  single  □
    CVP: Lowest: [ ]  Highest: [ ] cm H2O  CVP not available  □  single  □
    Mean arterial pressure: Lowest: [ ] [ ]  Highest: [ ] [ ] mm Hg  single  □
For each 6 hr block for the last 24 hrs record highest and lowest temperature and lowest SpO₂ and corresponding FiO₂ and Mean Airway Pressure. If only single temperature measurement for block, check “Single value” box. If no SpO₂ measured for block, check the “None” box.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Temp (°C)</th>
<th>Date/Time (If single value check box)</th>
<th>Site of Temp measurement</th>
<th>Low SpO₂ (pulse Ox) (%)</th>
<th>FiO₂ (%)</th>
<th>Mean airway pressure (cm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0601-1200</td>
<td>High:</td>
<td>☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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<td>None ☐</td>
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<td></td>
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<td>None ☐</td>
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<td>☐ Esophageal ☐ Urinary ☐ Peripheral ☐ IV</td>
<td>None ☐</td>
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</tbody>
</table>

In last 24 hours did patient receive?

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

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

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

Epoprostenol ☐ Nitric Oxide ☐ Total hours administered: ☐

Vasopressor support in last 24 hrs ☐ Yes ☐ No If No proceed to question 18.

(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: ☐

Laboratory data (if only one value, record in “Lowest” field and click “Single” box; if no data, click “None” box):

CBC values:

WBC: x1000/mm³ ☐ Single ☐, ☐, ☐, ☐ Lowest: ☐, ☐ Highest: ☐, ☐
Hgb: Lowest: ☐, ☐, ☐, ☐ g/dL Single ☐ None ☐
Hct: ☐, ☐, ☐, ☐ Lowest: ☐, ☐ Highest: ☐, ☐
Platelets: Lowest: x1000/mm³ ☐ ☐ ☐ ☐ None ☐
Serum Levels:

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<th>Highest</th>
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**Highest/Lowest finger stick glucose every 6 hrs for last 24 hrs (if only single value, enter in “Lowest” field and check “Single value” box; If no data, check “None” box:**

<table>
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<tr>
<th>Time Period</th>
<th>Lowest Glucose (mg/dL)</th>
<th>Date</th>
<th>Time</th>
<th>Highest Glucose</th>
<th>Date</th>
<th>Time</th>
<th>Single Value</th>
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</table>

If patient was extubated/UAB prior to Study Day 7, go to question 27.

**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
  - BiVent
  - PC-SIMV
  - VC-SIMV
  - SPN-PPS
  - PC-BIPAP
  - VC-MMV
  - SPN-CPAP
  - PC-APRV
  - PC-HFO
  - PC-MMV
  - Other ________________

- **SERVO**
  - PC-CMV
  - VC-CMV
  - SPN-CPAP/PS
  - PC-AC
  - VC-AC
  - PS
  - PC-SIMV
  - VC-SIMV
  - CPAP
  - PC-APRV
  - PRVC
  - PRVC-SIMV
  - PC-APRV
  - NIV

**Extubated:** □ Yes □ No  If Yes, Date/Time of extubation: __________/________/________ 02:00-23:59
ARDSNet Ventilation Adherence Data (if still intubated and mechanically ventilated):

24 Measured Tidal Volumes:  
Lowest:  
Highest:  

25 Estimated hours patient ventilated with tidal volume > 7 ml/kg  

26 Applied PEEP:  
Lowest:  
Highest:  

27 Mean airway pressure:  
Lowest:  
Highest:  

Lung Physiology Parameters (recorded 0600 to 1000 day 3 post-randomization; If no data available, check “No values” box. If patient not intubated, check “Not intubated” box)

28 Plateau Pressure:  
Lowest:  
No values:  
Not intubated:  

29 PaO₂/FiO₂:  
Lowest:  
%Highest:  

Single Value:  
None:  

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

Fluid Management:

30 Total Intake since randomization:  

31 Total Output since randomization (include dialysis/CRRT):  

32 Plasma sample collected:  
Yes  
No  

33 Blood collected:  
Processed:  

34 Number 0.5 ml aliquots:  
1  2  3  4  5  6  7  8  9  10  

35 Date/Time placed in -80°C freezer:  

36 Location in freezer:  
Temperature reading on freezer:  

4 Site ID  
Patient ID  
Letter Code  

CHILL-pilot RCT  
Day 07 Data (Ver. 1.1)
Unassisted Breathing Check list (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 (0700 to 0700) 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: 

2. Spontaneous Breathing Trial performed? □Yes □No

3. Mode used for SBT: □PSV ___ / ___ cm H2O □CPAP ___ cm H2O □T-piece □trach collar

4. Duration of SBT prior to removal of mechanical ventilation: ___, ___ hours

5. Regarding SBT:
   1. Was SpO2 ≥ 90% and/or PaO2 ≥ 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. Data entry completed by ________________ Date/Time: 

7. Continuous unassisted breathing through study day 28: □ Yes □ No

8. If No, Date/Time and reason for re-initiation of ventilation

9. Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ___
Transition to Unassisted Breathing Checklist #2:

1. Data entered by _____________________ Date/Time: ___________________________
2. Spontaneous Breathing Trial performed? □ Yes □ No
3. Mode used for SBT: □ PSV ___ / ____ cm H₂O □ CPAP ___ cm H₂O □ T-piece □ trach collar
4. Duration of SBT prior to removal of mechanical ventilation: hours
5. Regarding SBT:
   1. Was SpO₂ ≥ 90% and/or PaO₂ ≥ 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. Data entry completed by _____________________ Date/Time: ___________________________

7. Continuous unassisted breathing through study day 28: □ Yes □ No

8. If No, Date/Time: ___________________________ and reason for re-initiation of ventilation

9. Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ___________
Transition to Unassisted Breathing Checklist #3:

1. Data entered by ____________________ Date/Time: _______________________

2. Spontaneous Breathing Trial performed? □ Yes □ No

3. Mode used for SBT: □ PSV ______ / _____ cm H₂O □ CPAP _____ cm H₂O □ T-piece □ trach collar

4. Duration of SBT prior to removal of mechanical ventilation: hours ______

5. Regarding SBT:
   1. Was SpO₂ ≥ 90% and/or PaO₂ ≥ 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. Data entry completed by ____________________ Date/Time: _______________________

7. Continuous unassisted breathing through study day 28: □ Yes □ No

8. If No, Date/Time ______________________ and reason for re-initiation of ventilation ______

9. Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): ______
Transition to Unassisted Breathing Checklist #4:

1. Data entered by __________________________ Date/Time: 

2. Spontaneous Breathing Trial performed? □ Yes □ No

3. Mode used for SBT: □ PSV ___ / ___ cm H₂O □ CPAP ___ cm H₂O □ T-piece □ Trach collar

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

5. Regarding SBT:
   1. Was SpO₂ ≥ 90% and/or PaO₂ ≥ 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. Data entry completed by __________________________ Date/Time: 

7. Continuous unassisted breathing through study day 28: □ Yes □ No

8. If No, Date/Time and reason for re-initiation of ventilation 

9. Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing): □□□□
Transition to Unassisted Breathing Checklist #5:

1. Data entered by ________________ Date/Time:  

2. Spontaneous Breathing Trial performed?  □ Yes □ No

3. Mode used for SBT:  □ PSV ____ / ____ cm H₂O □ CPAP ____ cm H₂O □ T-piece □ trach collar

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

5. Regarding SBT:
   1. Was SpO₂ ≥ 90% and/or PaO₂ ≥ 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. Data entry completed by ________________ Date/Time:  

7. Continuous unassisted breathing through study day 28:  □ Yes □ No

8. If No, Date/Time and reason for re-initiation of ventilation

9. Number of ventilator-free days in this UAB period (days from 0800 to 0800 without any assisted breathing):  

---

5
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 (0700 to 0700) in which the patient is ICU-free.

1. Data entered by __________________________

2. Date/time (0-2400) of ICU discharge/transfer order:

3. Date/time of ICU discharge/transfer?

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: __________________________

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. Data entry completed by __________________________ Date/Time: __________________________

9. Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28
   [ ] Yes  [ ] No

10. If Yes, Date/Time when was cancellation/readmission?

11. 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): [ ]

1
Subsequent ICU Discharge #1 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:

3 Date/time of ICU discharge/transfer?

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:

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 Data entry completed by ____________________________ Date/Time:

9 Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28
   □ Yes □ No

10 If Yes, Date/Time when was cancellation/readmission?

11 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): _______
Subsequent ICU Discharge #2 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:

3. Date/time of ICU discharge/transfer?

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:

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. Data entry completed by ________________________ Date/Time:

9. Was discharge/transfer cancelled or patient readmitted to an ICU before study day 28
   ☐ Yes ☐ No

10. If Yes, Date/Time when was cancellation/readmission?

11. 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): ______
Subsequent ICU Discharge #3 Checklist
(fill out one form for each ICU discharge within the first 28 days)

Form completed by __________________________

Date/time (0-2400) of ICU discharge/transfer order: __________________________

Date/time of ICU discharge/transfer? __________________________

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

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

If no, date last on ventilator: __________________________

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

Result of MOCA: /30 points ______

Data entry completed by __________________________ Date/Time: __________________________

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

If Yes, Date/Time when was cancellation/readmission? __________________________

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): ______
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: [ ]

3 Date/time of ICU discharge/transfer? [ ]

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: [ ]

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 Data entry completed by ___________________ Date/Time: [ ]

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

10 If Yes, Date/Time when was cancellation/readmission? [ ]

11 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): [ ]
Day 28 Data

1 Form completed by: ____________________________

2 Vital status  □ Alive  □ Dead

3 If Dead Date/Time of death:

   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 24 hours?  □ Yes  □ No
If No, date last on ventilator:

5 Is the patient still in the ICU?  □ Yes  □ No
If no, date of transfer or discharge:

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 Calculation of 28-day Ventilator-free days (VFDs):
   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 Calculation of 28-day ICU-free days (ICU-FDs):
   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: __________
Hospital Discharge

1 Form completed by: ____________________________

2 Date of hospital discharge?

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:

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  ____________
1. Did the patient have any Adverse Events?  
   - [ ] Yes  
   - [ ] No

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<th>AE #3</th>
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<td>with sequelae</td>
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<td>Recovering/resolving</td>
<td>Recovering/resolving</td>
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<td>15 Assessment made by investigator name</td>
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<td>16 Date of Assessment</td>
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</table>
## 60 Day-Telephone Contact

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

<table>
<thead>
<tr>
<th>Contact Attempt</th>
<th>Date of Contact Attempt</th>
<th>Time (24hr)</th>
<th>Name of caller</th>
<th>Contact Occurred</th>
<th>Outcome if no contact</th>
</tr>
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<tbody>
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<td>□ 3 Left Message</td>
</tr>
<tr>
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<td>□ 1 Yes</td>
<td>□ 1 No answer</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
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<td></td>
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<td>□ 3 Left Message</td>
</tr>
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<td>#3</td>
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<tr>
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<td></td>
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<td></td>
<td>□ 2 Left Voice message</td>
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</tr>
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<td>#4</td>
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<td>□ 3 Left Message</td>
</tr>
</tbody>
</table>

2. **Was information obtained directly from the study patient? □ Yes □ No**

3. **If No, name of person who provided information: ____________________________**

4. **Relationship to subject: ____________________________**

5. **Was this individual the Legal Authorized Representative? □ Yes □ No**
**Telephone Contact (continued)**

<table>
<thead>
<tr>
<th>QUESTION(S) TO BE ASKED</th>
<th>☐ Yes</th>
<th>☐ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Is the patient still alive?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ambulating without assistance?</td>
<td></td>
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</tr>
<tr>
<td>2. Need mechanical ventilation for any part of the day (other than treatment for obstructive sleep apnea)</td>
<td>☐ Yes</td>
<td>☐ No</td>
</tr>
<tr>
<td>3. Need supplemental oxygen</td>
<td>☐ Yes</td>
<td>☐ No</td>
</tr>
<tr>
<td>4. Location of patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Home</td>
<td></td>
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</tr>
<tr>
<td>☐ Acute Care Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Rehab</td>
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<td></td>
</tr>
<tr>
<td>☐ LTAC</td>
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</tr>
<tr>
<td>☐ Supervised living</td>
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<td></td>
</tr>
</tbody>
</table>

COMMENTS:

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11. FORM COMPLETED BY: ___________________________ DATE: __________/______/______
## 90 Day-Telephone Contact

<table>
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<tr>
<th>Contact Attempt #1</th>
<th>Date of Contact Attempt</th>
<th>Time (24hr)</th>
<th>Name of caller</th>
<th>Contact Occurred</th>
<th>Outcome if no contact</th>
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<tbody>
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<table>
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<th>Contact Occurred</th>
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<td>□ 1 No answer</td>
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<td>□ 2 Left Voice message</td>
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<td>□ 0 No</td>
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<td>□ 4 Line Busy</td>
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<table>
<thead>
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<th>Time (24hr)</th>
<th>Name of caller</th>
<th>Contact Occurred</th>
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<table>
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<th>Time (24hr)</th>
<th>Name of caller</th>
<th>Contact Occurred</th>
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---

2Was information obtained directly from the study patient? □ Yes □ No

3If No, name of person who provided information: ______________________________

4Relationwhip to subject: ______________________________

5Was this individual the Legal Authorized Representative? □ Yes □ No
### Telephone Contact (continued)

<table>
<thead>
<tr>
<th>QUESTION(S) TO BE ASKED</th>
<th>□ Yes</th>
<th>□ No</th>
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<tbody>
<tr>
<td>6. Is the patient still alive?</td>
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</tr>
<tr>
<td>7. Ambulating without assistance?</td>
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<td>8. Need mechanical ventilation for any part of the day (other than treatment for obstructive sleep apnea)</td>
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<td>9. Need supplemental oxygen</td>
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<td>10. Location of patient</td>
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<tr>
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<td>Supervised living</td>
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**COMMENTS:**

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

**FORM COMPLETED BY:** ________________________________ **DATE:** __________/______/______

MONTH D D Y Y Y Y