Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis

ACRONYM: ***CLOVERS***

VERSION ***VIII***

PROTOCOL CO-CHAIRS
IVOR DOUGLAS, MD
NATHAN I. SHAPIRO, MD, MPH

PROTOCOL COMMITTEE
Roy G Brower, MD
Samuel M. Brown, MD
Ben P deBoisblanc, MD
Matthew C Exline, MD
Adit A. Ginde, MD
Colin K Grissom, MD
Doug Hayden PhD
Alan E. Jones, MD
Kathleen Liu, MD
Chadwick D Miller, MD
Katie Oldmixon, RN
Pauline K Park, MD
Lora Reineck, MD
Todd W Rice, MD
Nancy Ringwood, BSN
Wesley H. Self, MD
Matthew Semler, MD
Jay S Steingrub, MD
Daniel Talmor, MD
B. Taylor Thompson, MD
Donald M. Yealy, MD

ADVISORS TO PROTOCOL
Rinaldo Bellomo, MD
Stephen Macdonald, MD

Table of Contents

1. Abbreviations and Definitions

1.1 Abbreviations

ARDS = Acute Respiratory Distress Syndrome

BiPAP = Bilevel Positive Airway Pressure

BUN = Blood Urea Nitrogen

CCC = Clinical Coordinating Center

DSMB = Data Safety Monitoring Board

FACTT = Fluid and Catheter Treatment Trial

FiO_2 = Fraction of Inspired Oxygen

GCS = Glasgow Coma Scale

ICU = Intensive Care Unit

IL-6 = Interleukin 6

IL-8 = Interleukin 8

INR = International Normalized Ratio

ITT = Intent to Treat

KDIGO = Kidney Disease Improving Global Outcomes

LAR=Legally Authorized Representative

NHLBI = National Heart Lung and Blood Institute

PETAL = Prevention and Early Treatment of Acute Lung Injury

P/F = PaO_2/FiO_2 ratio

S/F = SpO_2/FiO_2 ratio

SOFA = Sequential Organ Failure Assessment

SBP = Systolic Blood Pressure

SpO_2 = Oxygen Saturation via pulse oximetry

SUSAR = Serious and Unexpected Suspected Adverse Reactions

SAEs= Serious Adverse Events

VFD = Ventilator-free Days

WBC = White Blood Cell count

1.2 Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.

Adverse reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse reactions where there is a reason to conclude that the study intervention caused the event.

Assisted Ventilation (or Assisted Breathing): any level of ventilatory support at pressures higher than the unassisted breathing thresholds.

Home: Level of residence or health care facility where the patient was residing prior to hospital admission.

Intention to Treat (ITT): All eligible and consented patients who undergo randomization will be included in the ITT cohort for the purposes of analyzing the primary and secondary study outcomes.

Invasive Mechanical Ventilation: Assisted ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube.

Legally Authorized Representative: An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

Mortality prior to discharge home before day 90: This primary outcome includes deaths from all causes following randomization in any heath care facility prior to discharge home until study day 90. Study subjects still in a health care facility at study day 91 are considered alive for this endpoint.

Funding: National Institutes of Health (National Heart Lung and Blood Institute)

SAEs: Serious Adverse Events Adverse events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure

Sponsor: The Clinical Coordinating Center at Massachusetts General Hospital

Study day: The day of randomization is study day zero. The next day is study day one etc.

Study hospital: Defined as the hospital where the patient was randomized and enrolled.

Study withdrawal: Defined as permanent withdrawal from study before completion of study activities. If a patient or surrogate requests withdrawal from the study the clinician should seek explicit permission to continue data collection.

Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction (21 CFR 312.32(a)).

Suspected Unexpected Serious Adverse Reaction (**SUSAR**) An adverse reaction that is both unexpected (not consistent with the risks outlined in the protocol or investigator brochure), serious, and meets the definition of a Suspected Adverse Reaction

UAB (Unassisted Breathing): Spontaneously breathing with face mask, nasal prong oxygen, room air, T-tube breathing, tracheostomy mask breathing, CPAP ≤ 5 without PS or IMV assistance, or the use of noninvasive ventilation solely for sleep-disordered breathing

2. Trial Summary

2.1 Title

Crystalloids **L**iberal **O**r **V**asopressors **E**arly **R**esuscitation in **S**epsis **(CLOVERS)**

2.2 Objective

Primary Objective: To determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

2.3 Hypothesis

Primary Hypothesis: Restrictive (vs liberal) fluid treatment strategy during the first 24 hours of resuscitation for sepsis-induced hypotension will reduce 90-day in-hospital mortality.

2.4 Study Design

Study Design: Multicenter, prospective, phase 3 randomized non-blinded interventional trial of fluid treatment strategies in the first 24 hours for patients with sepsis-induced hypotension.

1. We will emphasize early screening and protocol initiation, and enroll a maximum of 2320 patients with suspected sepsis-induced hypotension.
   - ✓ All patients will receive at least 1 liter of fluids prior to meeting study inclusion criteria (and no more than 3 liters prior to randomization).
   - ✓ Patients will be enrolled within 4 hours of meeting study inclusion criteria
   - ✓ Balanced crystalloid solution (such as lactated Ringers, Hartman's solution, Plasmalyte or Normosol) recommended

2. Restrictive Fluids (Early Vasopressors) Group (See Protocol Schema Appendix A)
   - ✓ Norepinephrine will be used as preferred vasopressor and titrated to achieve mean arterial pressure (MAP) between 65 mmHg and 75 mmHg
   - ✓ "Rescue fluids" recommended as 500 ml boluses if predefined rescue criteria are met

3. Liberal Fluids (Fluids First) Group (See Protocol Schema Appendix A)
   - ✓ Additional 2-liter intravenous fluid infusion upon enrollment with a clinical evaluation at the end of the first liter
   - ✓ Administer 500 ml fluid boluses for fluid triggers until 5 liters administered (includes BOTH pre-randomization and post-randomization intravenous fluids), or development of clinical signs of acute volume overload develop
   - ✓ Return to care without study guidance after 5 liters of fluid (this includes BOTH pre-randomization and post-randomization intravenous fluids) are administered

"Rescue vasopressors" recommended for persistent hypotension/hypoperfusion and acute volume overload, if other "rescue" criteria are met, or if the judgment of the clinical team is that vasopressors are thought to be in the best interest of the patient during fluid administration to support blood pressure and then weaned off as feasible once the fluid boluses have had their effect.

4. Attending physician and clinical provider oversight
   - ✓ The attending physician must agree that both the CLOVERS Early Vasopressor and Fluid First approaches are consistent with good medical care for their patient prior to enrollment.
   - ✓ The attending physician will be informed that fluids or vasopressors can be used at any time if they are thought to be in the best interest of the patient.

5. Other care
   - ✓ Other elements of care (e.g. antibiotics, ventilation strategies, etc.) will be recommended to reflect current "best-practice" where feasible and appropriate

2.5 Inclusion Criteria

1. Age ≥ 18 years
2. A suspected or confirmed infection (broadly defined as administration or planned administration of antibiotics)
3. Sepsis-induced hypotension defined as systolic blood pressure < 100 mmHg or MAP < 65 mmHg or receiving a vasopressor infusion after a minimum of at least 1 liter of fluid (*Fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

2.6 Exclusion Criteria

1. More than 4 hours elapsed since meeting inclusion criteria
2. More than 24 hours elapsed since presentation to the hospital
3. Patient already received more than 3 liters of intravenous fluid (includes prehospital volumes)
4. Unable to obtain informed consent
5. Pregnancy
6. Hypotension suspected to be due to non-sepsis cause (e.g. hemorrhagic shock)
7. Blood pressure is at known or reported baseline level
8. Severe Volume Depletion from an acute condition other than sepsis.
   In the judgment of the treating physician, the patient has an acute condition other than sepsis causing (or indicative) of *severe volume depletion;
   Examples include: Diabetic ketoacidosis, high volume vomiting or diarrhea, hypersomolar hyperglycemic state, and nonexertional hyperthermia (heat stroke); severe is defined by the need for substantial intravenous fluid administration as part of routine clinical care

9. Pulmonary edema or clinical signs of new fluid overload (e.g. bilateral crackles, new oxygen requirement, new peripheral edema, fluid overload on chest x-ray)
10. Treating physician unwilling to give additional fluids as directed by the liberal protocol*****
11. Treating physician unwilling to use vasopressors as directed by the restrictive protocol*****.
12. Current or imminent decision to withhold most/all life-sustaining treatment; this **does not** exclude those patients committed to full support except cardiopulmonary resuscitation
13. Immediate surgical intervention planned such that study procedures could not be followed
14. Patient no longer meets the hypotension inclusion criterion (no available SBP < 100 or MAP < 65 within 30 minutes of randomization or not receiving a vasopressor infusion)
15. Prior enrollment in this study

*Patients will be excluded if the attending physicians believes that either study arm is not good clinical care for his/her patient in their clinical judgement (see Appendix I)

2.7 Randomization and Initiation Time Window

All patients must be enrolled and randomized within 4 hours of meeting inclusion criteria. Patients may become eligible in the ED, hospital ward, or ICU.

2.8 Primary Endpoint

The primary outcome is all-cause mortality prior to discharge home before day 90.

2.9 Secondary Endpoints

1. 28-day organ support free days (alive and without mechanical ventilation, new renal replacement or vasopressors; vasopressors prior to 48 hours excluded)
2. 28-day ventilator free days
3. 28-day renal replacement free days (new renal replacement therapy)
4. 28-day vasopressor free days (vasopressors prior to 48 hours excluded)
5. 28-day ICU free days
6. 28-day hospital free days to discharge home
7. Initiation of mechanical ventilation to day 28
8. Initiation of renal replacement therapy to day 28
9. Change in creatinine-based KDIGO stage between baseline and 72 hours
10. Change in SOFA score between baseline and 72 hours
11. 90-day all-cause mortality
12. Development of ARDS within 7 days
13. Change in Interleukin-6 (IL-6) levels
14. New onset atrial or ventricular arrhythmia to day 28

2.10 Process of Care Metrics

Process of Care Metrics: We will assess whether the proposed intervention has effectively altered care as intended by measuring:

- ✓ Total intravenous fluids administered over initial 6 hours
- ✓ Total intravenous fluids administered over initial 24 hours
- ✓ Proportion receiving vasopressors and timing of vasopressor initiation within 24-hour study period
- ✓ Total fluids administered prior to initiation of vasopressors

2.11 Sample Size/Interim Monitoring

1. Randomization 1:1; two-sided alpha 0.05.
   A total of 2320 patients are needed to detect a 4.5% absolute mortality difference between treatment groups with 90% power assuming 15% mortality in the liberal fluids group. The principal analysis will be intent-to-treat, based upon randomization assignment.
2. There will be a protocol feasibility assessment phase at the approximately100-patient mark, and then after approximately 100 enrolled patients are available after any protocol changes for 2 more evaluation assessments. Aggregate data blinded to outcomes will be used to assess patient accrual, treatment protocol compliance, and separation of intravenous fluid and/or vasopressor administration. Protocol adjustments may be made at each of these patient marks to optimize the protocol. The study may be halted during the feasibility assessment phase for failure to meet pre-specified stopping guidelines
3. Trial progress will be evaluated by an independent Data and Safety Monitoring Board (DSMB) to determine whether the study should stop for superiority of either the liberal or restrictive fluid strategies; or, for projected trial futility. (See Appendix B) There will be two interim analyses and a final analysis conducted when approximately each successive 1/3 of the patients have been enrolled.

3. Trial Description

3.1 Background

Fluid resuscitation is a cornerstone for initial treatment of patients with sepsis-induced hypotension or septic shock[1]. In a 2001 landmark trial, Dr. Emmanuel Rivers et al[2] demonstrated that early identification and aggressive resuscitation of septic shock patients, as delivered through the Early Goad Directed Therapy (EGDT) algorithm, led to a substantial mortality reduction as compared to “usual care” at that time. This trial broadly led to a re-examination of clinical practice and is considered to have facilitated a more timely, aggressive, and compulsive approach to sepsis care. More recently, three large trials of Early Goal Directed Therapy (ProCESS[3], ARISE[4], and ProMISe[5]) demonstrated resuscitation targeting physiologic endpoints (central venous pressure (CVP), saturation of mixed venous oxygen (SvO_2), and mean arterial pressure (MAP)) was not superior to current usual care. Most patients in both the intervention and control groups of these trials received early sepsis

identification, prompt antibiotics, and large fluid boluses early in the resuscitation.[3-5] Furthermore, mortality in both the intervention and control groups was lower than historical septic shock mortality rates, leading many readers to conclude that advances in usual care for sepsis since the original Rivers trial led to improved outcomes over time.[6] However, the contribution of large volume fluid resuscitation toward declining sepsis mortality is unclear, and the optimal use of intravenous (IV) fluids and vasopressors remains controversial, with some advocating for liberal use of fluids to maintain blood pressure[2, 7-9] and others advocating for more restrictive use of fluids and relying on vasopressors to maintain blood pressure.[10, 11] Currently, no high quality data exist to guide clinical decision making on the volume of fluid to administer during early septic shock resuscitation. Equipoise clearly exists. This trial will directly compare early sepsis resuscitation with large IV volumes coupled with rescue vasopressors as opposed to early vasopressors coupled with rescue fluids.

3.2 Rationale for Liberal Fluid Approach

A "liberal" fluid approach to septic shock management is characterized by the administration of several liters (> 30 ml/kg) of IV crystalloid to an adult during the initial resuscitation period and assumes intravascular volume expansion is more beneficial than other potential treatment approaches for hypotension. Vasopressor medications are added if the patient is profoundly hypotensive (e.g. a systolic blood pressure < 70 mmHg) or remains hypotensive despite large volume fluid resuscitation. This liberal fluid approach is the predominant strategy used in U.S. emergency departments, and has been encouraged by the Surviving Sepsis Campaign Guidelines [1], advocates of Early Goal Directed Therapy[2, 7, 8], and the National Quality Forum Severe Sepsis and Septic Shock Management Bundle (NQF #0500)[9], which has been endorsed by Centers for Medicare and Medicaid Services (CMS) as the SEP-1 core measure.[12]

The physiologic rationale for liberal fluid administration is based on the notion that septic shock causes loss of vasomotor tone and intravascular volume depletion from loss of fluid into the extravascular space via leaky capillaries.[12] Crystalloid administration bolsters fluid volume within dilated vessels and replaces fluid lost into the extravascular space, potentially increasing cardiac pre-load, stroke volume, and cardiac output, thereby leading to improved blood pressure and tissue perfusion. Reversal of hypotension with fluid boluses allows clinicians to avoid vasopressors, which have the potential to cause cardiac arrhythmias, tissue ischemia, and soft tissue damage from extravasation.[13]

Several clinical studies during the past two decades have suggested that large volume fluid resuscitation is associated with improved outcomes for patients with septic shock. In the 1990s, in-hospital mortality rates for septic shock were typically reported in the 40%-50% range for hospitals in developed countries.[8] In 2001, Rivers et al.[2] published results of a single-center trial showing lower in-hospital mortality with Early Goal Directed Therapy, a protocolized resuscitation strategy targeting CVP, SvO_2 and MAP, compared to usual sepsis resuscitation at the time (mortality: 30.5% vs 46.5%). The Early Goal Directed Therapy protocol included instructions to administer IV fluid boluses to achieve a CVP > 8 mmHg. This led to patients in the Early Goal Directed Therapy group receiving larger fluid volumes during the first six hours of

treatment than those in the usual care control group (mean volume of IV fluid administration: 5.0 liters vs 3.5 liters).[2] Following this trial, the practice of early large-volume fluid resuscitation was widely adopted.[14] Observational studies at many institutions during the past 15 years demonstrated that efforts to implement Early Goal Directed Therapy protocols – even if full protocol adherence was incomplete and low - were associated with larger volumes of fluid administration and lower mortality.[8] However, most of these studies involved implementation of a multifaceted bundle of sepsis care, had varying and low compliance with specific aspects of the protocol, and the effects of different volumes of fluid resuscitation were not separated from the effects of other bundle components, such as routine lactate measurement, early antibiotics, and specialized sepsis response teams.[15, 16]

Results of three large multicenter trials evaluating Early Goal Directed Therapy for early septic shock resuscitation, including ProCESS[3], ARISE[4], and ProMISe[5], published in 2014-2015 demonstrated no significant difference in mortality between patients initially resuscitated according to Early Goal Directed Therapy versus usual care. The volume of intravenous fluid administration during the initial 6 hours of treatment in the Early Goal Directed Therapy group was only slightly larger than the usual care group in each of these trials (mean fluid volume: approximately 4.3 – 5.3 liters in all groups of all trials), indicating that early, large volume fluid resuscitation had been incorporated into usual care. Therefore, the ProCESS, ARISE, and ProMISe trials did not directly provide data on the comparative effects of a liberal versus restrictive fluid strategy or give precise guidance on an optimal dose of IV fluids. However, these trials did demonstrate that the short-term mortality risk for patients with septic shock today (approximately 18% – 25%) declined compared to the 1990s (approximately 40% - 50%), a period during which early large volume fluid resuscitation was not routine. These data suggest the possibility, though not directly proven, that a more liberal early fluid strategy may have contributed to declining sepsis mortality over time.

3.3 Rationale for Restrictive Fluids Approach

A “restrictive” fluid approach to septic shock management is characterized by the administration of modest fluid volumes (< 20 ml/kg) to reverse overt intravascular volume depletion coupled with the use of vasopressors early in the resuscitation. The primary strategy to maintain blood pressure and systemic perfusion is vasopressor titration, with fluid boluses used to augment vasopressor therapy when signs of tissue hypoperfusion persist despite high vasopressor doses, such as norepinephrine >20 mcg/min (0.25 mcg/kg/min in an 80 kg adult). Historically, the common practice of requiring central venous access for vasopressor infusion hampered vasopressor use early in care.[17] However, emerging data suggest norepinephrine can be safely administered through large peripheral intravenous catheters,[18, 19] which facilitates vasopressor use as a viable option for early sepsis resuscitation.

The physiologic rationale for a restrictive fluid strategy notes that IV crystalloid administration transiently increases intravascular volume but also leads to worsening extravascular fluid leakage (edema). The latter may interfere with cellular function in the kidneys, liver, heart and lungs.[11] Several days of diuresis after shock resolution are often necessary to remove this excess fluid generated by an initial liberal fluid strategy.[20] Meanwhile, vasopressors can

reverse the loss of vasomotor tone and increase cardiac output without burdening tissues with excess extravascular fluid.[21] Physiologic studies suggest that 30-50% of septic shock patients do not have an increase in cardiac output with fluid boluses; and, when cardiac output does increase, it often only lasts for 30-60 minutes.[11, 22-24] Therefore, many septic patients treated aggressively with fluids potentially experience little benefit in terms of increased cardiac output but do experience significant negative consequences from tissue edema. Increased CVP from fluid boluses may actually decrease tissue perfusion by narrowing the gradient between mean systemic pressure and venous pressure, which drives tissue perfusion.[25] Furthermore, some have hypothesized that the peripheral vasoconstrictive response to shock is beneficial by selectively providing perfusion to essential organs at the expense of non-vital tissues; rapid reversal of this adaptive physiologic response with fluid boluses may be deleterious.

More recent clinical studies suggest that large fluid boluses as an initial therapy for septic shock may have deleterious effects on patient outcomes. Maitland et al.[26] published the FEAST study in 2011. In this trial conducted in sub-Saharan Africa, septic children randomized to initial therapy with IV crystalloid boluses had higher 48-hour mortality than those treated without fluid boluses (10.5% vs 7.3%). While results of this trial that included young children (median age 2 years) who were predominately infected with malaria are not directly generalizable to adults in U.S. emergency departments and ICUs, these data do challenge the paradigm that large volume fluid resuscitation is universally beneficial to septic patients. In the recently-published CLASSIC trial of 151 adults with septic shock, Hjortrup et al[10] found that after an initial fluid bolus of ≥ 30 ml/kg, a restrictive fluid strategy was associated with less total fluid volume administered and lower risk of acute kidney injury than a usual care liberal fluids strategy; mortality was not statistically different between groups in that small trial.

3.4 Equipoise Exists Between Liberal and Restrictive Fluid Approaches?

Despite significant progress during the past two decades, morbidity and mortality from septic shock remain high, with opportunity for additional improvement.[14, 3-5] Although large volume fluid boluses are commonly used during the initial resuscitative phase of septic shock management, this practice is based on low quality evidence.[14, 11] Challenging the liberal fluid strategy is appropriate at this time because patient outcomes remain suboptimal, and there is strong physiologic rationale for a restrictive fluid, vasopressor-centered strategy.[11, 20-22, 24, 23, 25] While recent clinical studies suggest a restrictive strategy may be superior to a liberal strategy,[10, 26] no large, rigorous trial has compared these approaches. Therefore, we will conduct a phase III randomized controlled trial comparing all-cause 90-day in-patient mortality with a liberal versus restrictive fluid approach for early management of sepsis-induced hypotension.

3.5 Objectives

Primary Objective: To determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

Primary Hypothesis: Restrictive (vs liberal) fluid treatment strategy during the first 24 hours of resuscitation for sepsis-induced hypotension will reduce 90-day in-hospital mortality.

3.6 Endpoints

3.6.1 Primary Outcome

The primary outcome is all-cause mortality prior to discharge home before day 90. "Home" is defined as a patient's place of residence prior to enrollment. Thus, if a patient is discharged to a location that is different from the place of residence prior to enrollment (e.g. rehabilitation facility or hospice) then the patient will be followed until they return to their original location, 90 days, or death, whichever comes first.

3.6.2 Secondary Outcomes

1. **28-Day Organ Support Free Days**
   Organ support free days is defined as a patient being alive and without assisted breathing, new renal replacement therapy, or vasopressors (beyond 48 hours). Patients will be followed for use of organ support to death, hospital discharge or study day 27, whichever comes first. Any day that a patient is alive and without organ support will represent days alive and free of organ support. Since there will be a bias in the protocols to place patients on vasopressors in the restrictive group, vasopressor use prior to 48 hours will be excluded from this calculation for both groups.

2. **28-day Ventilator Free Days (VFDs)**
   VFDs depend on both duration of ventilation and mortality through study day 28. In participants who survive 28 days, VFD is defined as 28 minus duration of ventilation. Duration of ventilation is counted from the first study day of assisted breathing through the last day of assisted breathing provided the last day is prior to day 28. Otherwise, it is counted from the first study day of assisted breathing through day 28. For participants discharged with assisted ventilation (e.g., to LTAC facility) prior to day 28, a phone call will be required to assess ventilator and vital status at day 28. Participants discharged prior to day 28 on unassisted breathing will be assumed to remain on unassisted breathing through day 28. Isolated periods of ventilation briefer than 24 hours for surgical procedures and ventilation solely for sleep disordered breathing do not count towards duration of ventilation. In participants who never require assisted breathing, duration of ventilation is zero. Participants who do not survive 28 days will be assigned zero VFD. VFD is undefined in participants with chronic/home mechanical ventilation (except solely for sleep disordered breathing) and they will be excluded from this analysis.

3. **28-day Renal Replacement Therapy Free Days**
   Renal replacement free days to day 28 are defined as the number of calendar days between randomization and 28 days later that the patient is alive and without new renal replacement therapy. We also follow the "last off" method. Patients who died prior to day 28 and those who receive renal replacement therapy for the entire first 28 days are assigned zero renal replacement free days.

4. **28-day Vasopressor Free Days**
   Vasopressor free days to day 28 are defined as the number of calendar days between day 2 (eligibility starting 48 hours post randomization) and 26 days later that the patient is alive and without the use of vasopressor therapy. We also followed the "last off" method. Patients who died prior to day 28 and those who receive vasopressor therapy for the entire first 28 days are assigned zero vasopressor free days.

5. **28-day ICU free days**
   ICU free days to day 28 are defined as the number of days spent alive out of the ICU to day 28.

6. **28-day hospital free days**
   Hospital free days to day 28 are defined as 28 days minus the number of days from randomization to discharge home. If a patient has not been discharged home prior to study day 28 or dies prior to day 28, hospital free days will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

7. **Initiation of mechanical ventilation to day 28**
   Patients who receive invasive mechanical ventilation via endotracheal or tracheostomy tube, except those intubated solely for a procedure and extubated within 24 hours, through to study day 28 meet this endpoint. Non-invasive mechanical ventilation will not be included as an outcome. This is a binary outcome.

8. **Initiation of renal replacement to day 28**
   Patients who receive (new) renal replacement therapy through day 28 will meet this endpoint. Patients with chronic renal replacement therapy initiated prior to the current sepsis illness will not be eligible to meet this endpoint.

9. **Change in creatinine-based KDIGO stage between baseline and 72 hours**
   Renal function will be assessed using the KDIGO staging system (serum creatinine criteria only; not urine output) between baseline and 72 hours to assess for de novo acute kidney injury (AKI) (e.g., meeting criteria for AKI by KDIGO criteria) or worsening AKI (e.g., increasing severity). Due to the potential influence of treatment assignment on urine output, as well as the potential for inaccurate urine output data in patients without indwelling urinary catheters, we will use only the KDIGO creatinine criteria. Patients on chronic renal replacement therapy will not be eligible for this endpoint determination.

10. **Change in SOFA score between baseline and 72 hours**
    We will calculate the SOFA score upon enrollment and at 72 hours using clinically available data. If a value is not available at baseline, it will be assumed to be normal. At the 72 hours assessment, if a value is missing then we will carry forward the closet previously known value. If a patient is intubated or heavily sedated at either 0 or 72 hours, the GCS will be omitted when calculating the change in score. If a patient was on renal replacement therapy prior to presentation, then the renal dysfunction component to the SOFA score will be omitted as well. (See Appendix C)

11. 90-day all-cause mortality

We will contact patients at day 90 to ascertain their survival status. This will be done by telephone contact with the patient or family members as well as a review of medical records and publicly available data sources. We will use the national death index as a final check for patient with whom we are unable to confirm their vital status through other means.

12. Development of ARDS within 7 days

We will determine the presence and severity of ARDS for each day of mechanical ventilation to day 7 using the following approach: for each ventilator day, if an ABG is available between 2:00 AM and 8:00 AM, measure P/F (PaO2, FiO2 and PEEP) for all ABGs during this time window daily to day 7. Or, for ventilator days that no ABG available between 2:00 AM and 8:00 AM, determine lowest imputed P/F from measured S/F (SpO2, FiO2, and PEEP).

For participants with P/F <300 or imputed P/F <300, FiO2 ≥40%, and PEEP ≥5 cm H2O, determine if hypoxemia is valid, acute, and not fully explained by CHF or fluid overload. If yes, local investigators will review the first CXR (or CT) performed on each ventilated day with valid P/F or imputed P/F <300 (to day 7). If no chest imaging studies are present that day, site investigators may review available imaging one day before or after to determine if ARDS imaging criteria met. ARDS imaging criteria are met if the images are consistent with ARDS (bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules). If equivocal, the reviewing investigator will adjudicate with additional investigators.

13. Change in Circulating soluble IL-6 levels over 72-hours

In order to assess the impact of the resuscitation strategy on the inflammatory response, we will collect blood specimens and measure circulating soluble IL-6 at enrollment, and then at 24, and 72 hours.

14. Supraventricular/ventricular tachycardia (SVT/VT) or new onset atrial fibrillation/flutter (AF) to day 28

The occurrence of one or more episodes (sustained for more than 1 minute for SVT and AF, > 15 seconds for VT) during through day 28 will be recorded.

3.6.3 Process of Care Metrics

1. Total intravenous fluids administered over first 6 hours after randomization
2. The total amount of intravenous fluids or blood products of any type administered from pre-randomization to 6 hours after randomization.
3. Total intravenous fluids administered over 24 hours after randomization
4. The total amount of intravenous fluids or blood products of any type administered from pre-randomization to 24 hours after randomization.
5. Proportion receiving vasopressors and timing of vasopressor initiation within 24-hour study period

    a. Proportion of patients receiving vasopressors within 24 hours will be calculated. Additionally, among patients who received vasopressors, the duration of time elapsed from randomization until the time of initiation of vasopressor medications within 24-hour protocol period will be recorded.
6. Total fluids administered prior to initiation of vasopressors
    a. This process of care metric will assess the amount of fluids administered prior to the first receipt of vasopressors. (patients on vasopressors prior to randomization excluded from this metric)

We will use a bedside flow-sheet as a data collection instrument to record fluid and vasopressor administration, with the indications for administration, during the 24-hour protocol period. This will detail the delivery of the study interventions and assess protocol compliance. The data will be reported to the protocol oversight committee (and disseminated to the sites as protocol compliance metrics) as aggregate per-arm data in a blinded fashion (e.g. descriptive numbers only without an "n" or any indication of outcome or clinical status). This will occur at the 100, 200, and 300 patient data completion marks as described in the feasibility evaluation phase (Section 8). After the feasibility evaluation phase, we will perform a simplified data collection of summary fluid and vasopressor administration during the 24-hour treatment period and the data will be distributed after the first 10 patients for any new site, and then quarterly, to allow treatment protocol adherence monitoring. Any site with deficient compliance and/or separation of treatment arms after the initial 10 patients or during the quarterly reports may receive re-education and/or be asked to cease enrollment.

The DSMB will also receive these data to assess the separation of intravenous fluid and/or vasopressor administration between study arms. The DSMB will review these data during the protocol feasibility phase, as well as during scheduled interim analyses as outlined in the statistical plan.

3.6.4 Subgroups for secondary analysis

1. Patients receiving chronic dialysis
2. Patients with history of chronic heart failure (as documented in past medical history)
3. Patients with qualifying SBP < 90 mmHg versus 90-100 mmHg at randomization
4. Patients age > 65 years of age
5. Patients with a clinically confirmed infection as a cause of hypotension at study enrollment (as assessed by the investigator using records available throughout hospitalization)
6. Patients with pneumonia as the etiology of sepsis
7. Stratification by SOFA score quartiles on enrollment
8. Patients enrolled in the ED (vs. wards or ICU)
9. Patient with a history of hypertension (as documented in past medical history or by the prescription of chronic medications)

4. Study Population and Enrollment

4.1 Number/Source Screening

The trial will accrue a maximum of 2,320 patients. Patients will be recruited from the EDs, ICUs and other acute care areas of the PETAL Network Clinical Centers. The overall strategy is to screen and approach patients/surrogates for consent and enrollment early.

4.2 Inclusion Criteria

1. Age ≥ 18 years
2. A suspected or confirmed infection (broadly defined by administration or planned administration of antibiotics)
3. Sepsis-induced hypotension defined as systolic blood pressure < 100 mmHg or MAP < 65 mmHg or receiving a vasopressor infusion after a minimum of at least 1 liter of fluid (*Fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

4.3 Exclusion Criteria

1. More than 4 hours elapsed since meeting inclusion criteria
2. More than 24 hours elapsed since presentation to the hospital
3. Patient already received more than 3 liters of intravenous fluid (includes prehospital volumes)
4. Unable to obtain informed consent
5. Pregnancy
6. Hypotension suspected to be due to non-sepsis cause (e.g. hemorrhagic shock)
7. Blood pressure is at known or reported baseline level
8. Severe Volume Depletion from an acute condition other than sepsis.
   In the judgment of the treating physician, the patient has an acute condition other than sepsis causing (or indicative) of *severe volume depletion;
   Examples include: Diabetic ketoacidosis, high volume vomiting or diarrhea, hyperosmolar hyperglycemic state, and non-exertional hyperthermia (heat stroke); severe is defined by the need for substantial intravenous fluid administration as part of routine clinical care
9. Pulmonary edema or clinical signs of new fluid overload (e.g. bilateral crackles, new oxygen requirement, new peripheral edema, fluid overload on chest x-ray)
10. Treating physician unwilling to give additional fluids as directed by the liberal protocol*****
11. Treating physician unwilling to use vasopressors as directed by the restrictive protocol*****.
12. Current or imminent decision to withhold most/all life-sustaining treatment; this **does not** exclude those patients committed to full support except cardiopulmonary resuscitation
13. Immediate surgical intervention planned such that study procedures could not be followed

14. Patient no longer meets the hypotension inclusion criterion (no available SBP < 100 or MAP < 65 within 30 minutes of randomization or not receiving a vasopressor infusion)
15. Prior enrollment in this study

*Patients will be excluded if the attending physicians believes that either study arm is not good clinical care for his/her patient in their clinical judgement (see Appendix I)

4.4 Reasons for Exclusions

Criteria 1 and 2 exclude patients too late in the course of resuscitation to test the study hypothesis of early resuscitation strategies. Criterion 3 excludes patients who already exceed resuscitation volumes in excess of early goals the restrictive fluid group. Criteria 4 excludes patients where consent is unable to be obtained. Exclusion criterion 5 is included because there are not sufficient data to support either of the two treatment arms during pregnancy. Non-septic causes of shock (criterion 6) are excluded as the treatment differs from the study interventions. Criterion 7 excludes patients with normally low blood pressure who are unlikely to benefit from the blood pressure targets of this study. Criterion 8 excludes patients who are severely volume deplete who may require large volumes of intravenous fluids to treat non-sepsis conditions such that compliance with a restrictive fluid approach is not feasible. Criterion 9 excludes patients who may not tolerate the fluid goals of the liberal fluid group. Criterion 10 excludes patients where physicians are unwilling to administer additional fluids and thus would not be able to comply with the study treatment protocol. Criterion 11 excludes patients where physicians are unwilling to administer vasopressors and thus would not be able to comply with the study treatment protocol. Criterion 12 excludes patients who may not survive to important study endpoints or whose underlying condition or ventilator management complicates assessment of the secondary endpoint of ventilator free days. Investigators will not be able to execute study procedures in the operating room (criterion 13). Patients who have already been enrolled will not be allowed to participate twice (criterion 15).

4.5 Randomization and Study Initiation Time Window

All patients must be randomized within 4 hours of meeting inclusion criteria. The window for randomization begins at the time of meeting all inclusion criteria, regardless of patient location in the hospital.

4.6 Screening Log

All patients meeting inclusion criteria will be entered on a screening log. If the patient is not enrolled, the screening log will include information explaining why enrollment did not occur (e.g., exclusion criteria, attending physician denial, patient refusal) and baseline demographic information only will be collected.

4.7 Randomization

After obtaining a signed and dated informed consent from the subject or the subject's legal authorized representative (LAR), we will randomize subjects via the coordinating center web based randomization system. Each research coordinator will have a unique Personal Identification Number (PIN) to access the randomization system. Each subject will receive a computer-generated study ID number and study arm assignment to either the restrictive or liberal treatment arm. An emailed confirmation will be sent to the study site. Randomization will be stratified by the enrolling institution.

4.8 Minorities and Women

Access to women and racial minorities was considered by the NHLBI in selecting the PETAL Network Centers. The demographic profiles of the Centers selected for the Network show that the aggregate patient population contains representative proportions of minorities and women. Recruitment of minorities and women will be monitored by the PETAL Network Coordinating Center. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

5. Study Procedures

5.1 Restrictive Fluids Group (Early Vasopressors)

Restrictive Group Treatment Protocol
Once a patient is randomized to the restrictive fluids arm, the general approach will be to use vasopressors to treat hypotension as opposed to intravenous fluids. Maintenance fluids should not be used. Restoration of blood pressure and perfusion should be accomplished in accordance with the following protocol recommendations:

1. Initiate vasopressors (norepinephrine recommended first-line vasopressor) for MAP < 65 mmHg or SBP <90 mmHg
2. Titrate vasopressors to: 65 mmHg < MAP <75 mmHg
3. *"Rescue Fluids" are recommended, but not mandated, in 500 cc crystalloid boluses for <u>any</u> of the following:

    a. Severe hypotension (SBP <70 mmHg or MAP <50 mmHg)
    b. Refractory hypotension (MAP <65 mmHg) despite norepinephrine dose of at least 20 mcg/min or 0.25 mcg/kg/min or equivalent dose of another vasopressor (see Appendix E)
    c. Lactate > 4 mmol/L and rising from previous lactate, after at least 2 hours of therapy, in patients with serial lactates measured in usual care practice
    d. Sinus heart rate > 130 beats per minute for >15 minutes
    e. Evidence of extreme volume depletion from hemodynamic monitoring (if performed) based on any of the following:
        i. Maximal IVC diameter < 5mm; or

ii. Empty left ventricle on echo (i.e. left-ventricular end-diastolic area index < 5.5 cm^2/m^2 BSA) or
iii. Substantial volume responsiveness defined as stroke volume increase > 30% in response to a passive leg raise, fluid challenge, or positive pressure breaths during passive ventilation)

*Rescue fluids may be administered at any time if the clinical team believes that it is in the best interest of the patient

4. Patients should be monitored for volume overload, and fluids may be halted or reduced for clinical evidence of *symptomatic left atrial hypertension based on a clinical diagnosis by the treating or study physician.
    a. *Clinical features of symptomatic LA hypertension:
    signs and symptoms of fluid overload (or hydrostatic edema due to left atrial hypertension) include manifestations such as increased respiratory rate, increased use of accessory muscles of respiration, increased bilateral inspiratory crackles, increasing oxygen requirement, or pulmonary edema on chest x-ray likelycardiogenic in origin).
5. Return to care without study guidance for any of the following protocol endpoints:
    a. Suspicion of central (e.g. bowel) or peripheral (e.g. limb or digit) ischemia or presence of mottling
    b. > 24 hours have elapsed since protocol initiation

If fluids are used, a balanced crystalloid solution (such as lactated Ringers, Hartman's solution, Plasmalyte or Normosol) is recommended, normal saline is permitted. If a patient received less than 2 liters of fluids prior to randomization, then the patient may receive up to 2 liters of total fluid, including pre-randomization fluid, at the discretion of the clinical team in the restrictive arm without meeting rescue fluids criteria if they are assessed as volume deplete. However, once 2 liters of intravenous fluids have been infused, no additional fluids should be administered unless rescue fluids criterion is met or if the clinical team believes that additional fluids are in the best interest of the patient.

.

5.2 Liberal Fluids Group

Liberal Empiric Fluid Strategy

1. Initiate a 2000 cc crystalloid fluid infusion upon randomization (2000 cc to be complete within 180 minutes of randomization; clinician may extend infusion time at any point during the 2000 cc infusion if indicated for a given patient); monitor for signs of fluid overload
2. Clinical evaluation at the end of first 1000cc:
    - If blood pressure and heart rate have normalized (SBP ≥ 110 mmHg or MAP ≥ 70 mmHg and HR < 90 bpm) and clinical assessment is patient is volume replete, team

may forego second liter and move to 500cc boluses based on fluid triggers (#5 below); otherwise continue with second 1000cc infusion

3. Maintenance fluids should not be used.
4. Balanced crystalloid solution (such as lactated Ringers, Hartman's solution, Plasmalyte or Normosol) is recommended, normal saline is permitted.
5. Subjects receive a 500cc crystalloid fluid bolus for any of the following fluid triggers:
   a. SBP < 90 mmHg or MAP <65 mmHg
   b. Lactate > 4 mmol/l and rising in patients with serial lactates measured as part of usual care practices
   c. Reduced urine output (<30 cc/hour) for > 1 hour (except for ESRD patients)
   d. Sinus heart rate > 110 beats per minute
   e. Any measured/clinical assessment of volume status or volume responsiveness (e.g. echo, IVC measurement, CVP, etc) suggesting benefit from additional fluid (as defined by treating clinicians)
   f. Receiving vasopressors to maintain SBP ≥ 90 mmHg or MAP ≥ 65 mmHg
6. Patients should be monitored for volume overload, and fluids may be halted or reduced for clinical evidence of *symptomatic left atrial hypertension based on a clinical diagnosis by the treating or study physician.
   a. *Clinical features of symptomatic LA hypertension:
      signs and symptoms of fluid overload (or hydrostatic edema due to left atrial hypertension) include manifestations such as increased respiratory rate, increased use of accessory muscles of respiration, increased bilateral inspiratory crackles, increasing oxygen requirement, or pulmonary edema on chest x-ray likely cardiogenic in origin).
7. "Rescue vasopressors" recommended (in the form of norepinephrine infusion) for any of the following criteria:
   a. SBP < 70 mmHg or MAP < 50 mmHg for at least 5 minutes)
   b. Signs of volume overload (see above) with persistent hypotension/hypoperfusion
   c. Lactate > 4 mmol/L and rising from previous lactate, after at least 2 hours of therapy
   d. SBP < 90 mmHg after administration of 5000 cc of volume (includes all pre-randomization and post-randomization fluids or blood products) - transition to all decisions made by the clinical team at this point

*Vasopressors may be administered at any time if the clinical team believes that it is in the best interest of the patient, and then weaned off safely once the fluid boluses have their effect.

8. . Return to care without study guidance for any of the following:
   a. ≥ 5 liters of total IV fluids administered (including both pre-randomization and post-randomization intravenous fluids)
   b. > 24 hours have elapsed since protocol initiation
   c. Suspicion of central (e.g. bowel) or peripheral (e.g. limb or digit) ischemia or presence of mottling

5.3 The Use of Cardiac Ultrasound and Other Hemodynamic Monitoring Techniques

The use of advanced monitoring techniques, such as echocardiography, pulse contour analysis, bioimpedence and bioreactance, will be permitted but not mandated. If the clinician wishes to use these techniques, fluid administration should be titrated according to the CLOVERS study fluid protocol guidelines. In the restrictive group, clinical teams should refrain from adjusting treatment intervention outside the guidance provided whereby fluid boluses are administered only for the "Rescue Fluid" indications stated in the protocol (Section 5.1.c) unless the clinical team believes that alternative approaches would be in the best interest of the patient. In the fluid liberal group, we permit the clinician to use these techniques and allow for fluid boluses based on any provider-chosen metric of volume responsiveness.

6. Duration of the Protocol

The protocols are intended to run for 24 hours post randomization. Fluid management after 24 hours will be dictated solely by the clinical team.

6.1 Common Strategies for Both Study Groups

6.1.1 Permitted Fluid Types

Balanced crystalloid solution (such as lactated Ringers, Hartman's solution, Plasmalyte or Normosol) is preferred, any isotonic crystalloid is permitted. We recognize that there is theoretical rationale for using a balanced solution approach; however, given the lack of clear evidence identifying a superior approach, the type of fluid administered will be tracked but not mandated.

6.1.2 Antibiotics

Antibiotics should be administered as soon as possible, ideally within 1 hour from sepsis recognition. The selection of antibiotics will be guided by the clinical team and institutional protocols.

6.1.3 Ventilator Procedures

Standard institutional protocols should be used in accordance with low tidal volume ventilation best practice strategies.

Weaning: Since the time a patient achieves unassisted ventilation affects some secondary endpoints, and because recent evidence-based consensus recommendations have identified a best practice for weaning, a weaning strategy will be controlled by protocol rules in accordance with these evidence-based recommendations. This will assure similar weaning methods and provide potential benefit to both study groups. This weaning strategy is a simplified version of the protocolized weaning strategy used in prior ARDS Network studies (Appendix D).

6.1.4 Vasopressor Use

Vasopressor dosing should be titrated to achieve a 65mmHg < MAP < 75 mmHg. Vasopressor administration is permitted through either a central line or a 20 gauge or larger peripheral IV catheter.

Vasopressor Weaning: Since the time a patient achieves independence from vasopressors affects some secondary endpoints, we will use a slightly modified version of the vasopressor weaning protocol previously used in ARDSNet (Appendix E). This protocol will be distributed to the clinical team who will implement the protocol.

6.1.5 Fluid management After Protocol Conclusion (post 24 hours)

For both treatment arms, each site will revert to care without study guidance fluid for management practices 24 hours after randomization.

7. Data Variables and Specimens

7.1 Background Assessments

The following information will be collected from information available prior to randomization. If more than one value is available in the 24 hours prior to randomization, the value closest to the time of randomization will be recorded. If no values are available from the 24 hours prior to randomization, then values will be measured up to 24 hours. All values will be derived from clinically available data. (see Time of Events Schedule in Appendix F)

1. Demographic and Admission Data (including age, sex, race)
2. Pertinent Medical History and Physical Examination (including components of the Charlson co-morbidity score)
3. Height; gender; measured Body Weight (mBW); calculated predicted body weight (PBW); body mass index (BMI)
4. Location when inclusion criteria met: ED, ward, ICU, referring hospital
5. Vital signs: heart rate (beats / min), systemic systolic and diastolic BP (mmHg), body temperature (^{0}C), and oxygen saturation with FiO_2
6. Clinical laboratory testing results
7. Presumed site of infection
8. SOFA Score: as described in Appendix C
9. Attending physician assessment of CLOVERS eligibility (Appendix I)

7.2 Assessments during Protocol Phase

1. Type, timing, and volume of fluid administration
2. Type, timing, and dosing of vasopressor administration
3. Fluid inputs and outputs as clinically recorded
4. Identification of clinical signs and symptoms of fluid overload
5. Oxygen delivered by nasal cannula or face mask (including nasal high flow oxygen), non-invasive ventilation by tight fitting mask, and intubation

Together with changes in SOFA score and adverse events at 72 hours, these data will be reported as study process safety data to the DSMB quarterly or more often at the discretion of the DSMB.

7.3 Other Assessments and Data Collection

1. Vasopressor use over the hospitalization
2. Assisted ventilation over the hospitalization
3. New renal replacement therapy over the hospitalization
4. Daily fluid administration for the first 7 days
5. Daily fluid outputs (truncated for death or ICU discharge) for the first 7 days
6. Diuretic administration over the first 7 days
7. Clinical laboratory testing results during the first 72 hours post randomization
8. Results of microbiologic testing from samples taken over the first 72 hours after randomization
9. SOFA at hours 0 and 72

7.4 Specimen Collection

Plasma will be collected within 2 hours of randomization, at 24 hours, and at 72 hours, frozen, and stored at a biorepository for future research. When consent for genetic testing is specifically obtained, an additional 20 ml of whole blood for future RNA and DNA studies will also be collected. Total blood volume for these draws is approximately 30 ml/day, for a total of approximately 90 ml. Study samples will be sent to a central repository to be stored in accordance with good laboratory practices. Samples will be identified by a coded number during shipment and storage in the central repository.

7.5 Assessments after Hospitalization

1. Clinical assessment as to whether an infection was in fact the causative etiology of the hypotension:
   We will perform an assessment using all testing and records available during the hospitalization where a site investigator will make an assessment as to whether the hypotension at enrollment was likely due to an infection or not.

8. Feasibility Evaluation Plan

The protocol oversight committee, steering committee, and the DSMB will monitor the trial for feasibility during the initial phase of the trial (~300 patients will be assessed during 3 separate looks). After ~100 analyzable patients, the protocol committee will assess study arm separation, enrollment, and compliance using data from the trial. After reviewing these data, the protocol oversight committee may make recommendations to improve the trial, which would require approval by the steering committee and DSMB before implementation. The trial will continue to accrue patients without interruption while the feasibility evaluations occur. However, we will attempt to minimize the timeframe between the completion of 100 analyzable subjects and the recommendations and implementation of any study amendments. Further feasibility

assessments will occur after at least 100 additional patients are enrolled after any protocol modification (i.e., subjects 200 and 300 if no modifications; however, if as an example 30 patients were enrolled after an assessment at 100 patients but before the amended protocol was active, then the next assessment would occur after 230 patients were enrolled). To minimize time during this assessment phase, key data points such as fluid and vasopressor administration will be identified and completion for key elements will be required within 7 days of enrollment during the feasibility phase. Data completeness of these key elements will be monitored closely by the coordinating center. The analyses during the feasibility assessment phase will have no impact on the planned interim analyses and the final efficacy analysis.

Feasibility parameters (by treatment assignment) will include:

1. Subject accrual
2. Compliance with treatment protocols
3. Separation of the groups based on fluid and vasopressor administration data

The protocol committee, steering committee, and DSMB will have available demographic data, criteria for separation, study accrual, and compliance. The DSMB (only) will have available adverse event data.

At that point, the protocol committee will issue one of three recommendations to the steering committee for decision:

a) Continue without protocol modification,
b) Continue with protocol modification
c) Halt the trial.

The steering committee will be asked to approve the recommendation. Once the protocol committee and steering committee are in agreement, the responses will be provided to the DSMB, who will be charged with assessing whether there are any safety concerns. The DSMB will then have the opportunity to approve the recommendation or make additional recommendations. At the completion of the feasibility evaluation phase, if the study continues, all patients from the feasibility evaluation phase will be retained in the ITT analysis. No outcome data will be released in any form.

During the feasibility evaluation phase, the DSMB will also review:

1. Adverse Events
2. Central line use and any associated complications

8.1 Subject Accrual

The maximum sample size for the study is 2,320 subjects. We estimate that sample size is achievable in a timely fashion if we enroll an average of 1 patient/site/month, distributed across 50 enrolling sites. For the feasibility assessment phase, if the enrolling sites achieve >70% of this rate (> 0.7 patients/site/month), then the feasibility guideline for patient accrual will have been met. A site will be defined as “started” when the site indicates that they have begun

screening, and the #patients/month/sites will be calculated as the number of patients enrolled across all sites, divided by sum of the screening months among the site, and number of sites. A calendar month is defined by the number of days passed since the initiation of screening, divided by 30. If a site withdraws from the study, then they will stop contributing patients and calendar months.

8.2 Compliance with Fluid Management Protocols

Compliance with the hemodynamic protocol instructions and the safety of the protocol will be monitored by the protocol oversight committee and DSMB. Detailed treatment data in regards to intravenous fluid administration, vasopressor use, vital signs, and the presence of protocol defined criteria for fluid and vasopressor administration will be collected hourly for the first 24 hours by the sites on a detailed flow sheet. We will assess protocol compliance (defined as following the protocol rules based on vital signs and actions) for the first 6 hours, and then randomly sample 4 other 1-hour time-points during the 24-hour treatment period. The compliance rate will be defined as the proportion of correct actions among the total actions performed; or (correct actions)/(correct +incorrect actions) X100.

A "correct action" in the liberal group is defined as:

a. Administration of the initial 2-liter fluid infusion within the first 180 minutes (if documented clinical assessment leads to a decision to administer less than two liters during the initial infusion or if the infusion time is deliberately lengthened, this is considered a correct action)
b. Administration of a minimum 500cc fluid bolus when a "meets intervention criterion" is present
c. Vasopressor use in the presence of a "rescue criterion"
d. No fluid or vasopressor administration in the absence of a meets intervention criterion

An "incorrect action" in the liberal group is defined as:

a. Failure to administer the initial 2-liter fluid infusion within the first 180 minutes (if clinical evaluation is that patient has normalized - fluids may stop and be considered a correct action).
b. Failure to administer a 500cc fluid bolus when a "meets intervention criterion" is present and there is no contraindication (e.g. fluid overload or > 5 liters criteria already administered)
c. Use of a vasopressor in the absence of a "rescue vasopressors recommended" criterion
NOTE: In both arms, fluids or vasopressors can be used at any time if the clinical team feels they are in the best interest of the patient. An incorrect action as defined in the protocol is not a protocol deviation but would be considered non-compliant for the purposes of compliance monitoring.

A "correct action" in the restrictive group is defined as:

a. Initiation of vasopressors for SBP < 90mmHg and/or MAP <65mmHg within 60 minutes
b. Titration of vasopressors to maintain MAP ≥ 65mmHg
c. Administration of a 500cc fluid bolus in the presence of a "rescue fluid" criterion
d. Administration of fluid boluses to up to 2 liters of total fluid, including pre-randomization fluid,

at the discretion of the clinical team even where “rescue fluid” criteria are not met.

e. No fluid or vasopressor administration/titration in the absence of a meets intervention criterion

An “incorrect action” in the restrictive group is defined as:

a. Failure to initiate vasopressors for SBP < 90mmHg and/or MAP <65mmHg within 60 minutes
b. Failure to titrate vasopressors for sustained (greater than 30 minutes) MAP < 65 mmHg
c. Administration of intravenous fluid in the absence a “rescue fluids recommended” criteria
d. NOTE: In both arms, fluids or vasopressors can be used at any time if the clinical team feels they are in the best interest of the patient. An incorrect action is not a protocol deviation but would be considered non-compliant for the purposes of compliance monitoring.

The goal is to achieve > 70% compliance with instructions across enrolling sites. Summative data will be shared with the protocol committee, steering committee, and the DSMB. During this period, the protocol rules may be refined through iterative application and evaluation in the enrolling sites. If compliance is lower than 70%, but the separation of intravenous fluid volumes and/or vasopressor use between groups is met, amendments may be considered to try to improve compliance, but the trial will be considered feasible and will continue.

To maintain blinding to outcomes, the reports will be aggregated without reference to patient number. They will not include any information beyond the 24-hour treatment protocol period. The protocol oversight committee, PETAL steering committee and/or the DSMB may ask that detailed iterative refinement continue at each 100 patient data completion marks during this phase. The protocol oversight committee and PETAL steering committee may also recommend based on the data from the 100 or 200 patient data completion marks that no further protocol modifications are indicated.

8.3 Separation of Groups Based on Fluid and Vasopressor Administration Data

Experimental separation of patients in the restrictive versus liberal arms will be closely monitored over the course of the first 300 enrolled patients, with staged evaluations at 100, 200, and 300 patients to allow modification of experimental protocols to improve compliance and/or experimental separation. The trial can be stopped at 100, 200, or 300 patients based on the below criteria if there is evidence of lack of feasibility by enrollment rates, protocol compliance, and/or anticipated separation.

A decision to move to the next phase of the trial will be based on the likelihood of meeting 2 of the following 3 separation guidelines at the end of the trial:

1. Difference of 1000cc (or greater) fluid administered over the first 6 hours of the treatment protocol
2. Difference of 1000cc (or greater) fluid administered over the first 24 hours of the treatment protocol

3. Difference of 3 hours (or greater) of mean time of vasopressor use over the first 24 hours of the treatment protocol

During each look at the 100, 200, and 300 patient data completion mark we will have the opportunity to modify the protocol to optimize recruitment, protocol compliance, and treatment group separation. Fluid separation at 6 and 24 hours will be analyzed as follows: we will regress the log of the fluids administered on the treatment group and report the difference in the exponentiated means between the treatment groups and the confidence interval of this difference. This estimate is equivalent to the difference in the medians under the log-normal distribution, but the confidence limits are narrower due to the use of a parametric model. If the fit to the log-normal distribution is poor, we will estimate the difference in medians using quantile regression. If changes to significantly improve separation are not likely, and the upper end of a 90% confidence interval on the difference in medians is less than 1 liter, we will consider recommending that the study be stopped. (Note: This is equivalent to a test of the hypothesis HO that the true difference is 1 liter, against the one-sided alternative that the true difference is less than one liter, with a one-sided p-value of 0.1).

During these looks, we will exclude data from patients managed by a no-longer-current protocol (i.e., in the event that a protocol change was implemented at the 100 or 200-patient marks). The goal is to preserve 90% power to detect a true separation between treatment arms in the overall trial of 1000ml at 6 and 24 hours. The stopping criteria will be based on the pooled mean and standard error of the log-transformed-fluid volumes.

Based on preliminary from a comparable study in Africa analyzed in this manner, and assuming no change in fluid strategy at earlier looks, at the 300-patient look, the stopping criteria would have a 90% probability of stopping the trial if the true separation was 0.6 Liters or less. We will deploy an analogous approach to assess a difference in vasopressor use of at least 3 hours within the 24-hour protocol period.

If at least 2 of 3 feasibility guideline parameters for separation are met, the separation parameter guideline is met. If none of the guideline parameters are met, the protocol oversight committee will recommend termination of the trial. If one of the parameters is met, then the protocol oversight committee will examine the data to determine whether there is adequate separation or if a protocol modification is likely to lead to increased separation. At each of the feasibility assessment evaluations, the protocol oversight committee will determine whether separation guidelines are adequately fulfilled and make a recommendation to the SC, and DSMB. The DSMB has final decision-making authority.

8.4 Assessment of Eligibility Criteria

We will assess the subset of patients enrolled with a qualifying blood pressure of 90 ≤ SBP < 100 mmHg, and the guideline feasibility parameters in this subset of patients. If during the feasibility assessment, data suggest that this group does not meet protocol compliance or separation guideline parameters, then this group may be excluded from the rest of the trial.

9. Statistical Considerations

9.1 Sample Size and Stopping Rules for Primary Outcome

The primary outcome is intention-to-treat 90-day all cause in-hospital mortality, where in-hospital includes both study and discharge hospitals (i.e. transfer hospitals or LTAC). Subjects who are discharged home (defined as residence prior to admission) prior to day 90 will be assumed to be alive at day 90.

Sample size is based on a comparison of binomial proportions with an overall two-sided alpha level of 0.05 and power of 0.90. With 15% mortality rate in liberal fluid group and 10.5% mortality rate in the restrictive group, maximum required total sample size is 2320 subjects.

The presumed 15% mortality rate in the liberal fluid group is based on several recently published clinical trials (Process [2], ARISE [3], Promise [4]).

This trial will stop for efficacy of either the restrictive or liberal fluid strategy arm, or futility. The study is designed with a symmetric group sequential t^4 alpha error spending function and a symmetric non-binding t^4 beta error spending function, where t is the information time, defined as the ratio of the effective sample size at the time of the look to the eventual sample size.

We plan to have two interim analyses and one final analysis that will be approximately evenly spaced. However, the scheduling of the DSMB meetings may alter this schedule.

Tables 1 and 2 present the stopping boundaries at each of the two interim analyses if they are equally spaced. The tables present stopping boundaries as either a one-sided p-value or an observed mortality difference. Table 3 presents the probability of stopping at each stage under the null (no effect of fluid) and alternative (restrictive fluid reduces mortality from 15% to 10.5%) hypotheses respectively.

Table 1. Stopping Boundaries: One Sided P Values

Stage	Sample Size	Lower Efficacy	Lower Futility	Upper Futility	Upper Efficacy
1	773	0.0003086	.	.	0.99969
2	1547	0.00479	0.27413	0.72587	0.99521
3	2320	0.02361	0.02361	0.97639	0.97639

Table 2. Stopping Boundaries: Mortality Differences

Stage	Sample Size	Lower Efficacy	Lower Futility	Upper Futility	Upper Efficacy
1	773	-0.08194	.	.	0.08194
2	1547	-0.04384	-0.01016	0.01016	0.04384
3	2320	-0.02742	-0.02742	0.02742	0.02742

Table 3. Cumulative Stopping Probabilities

Stage	Stop: Reject Null Given Null	Stop: Accept Null Given Null	Stop: Reject Null Given Alternative	Stop: Accept Null Given Alternative
1	0.00062	0.00000	0.06136	0.00000
2	0.00988	0.45174	0.52878	0.01919
3	0.04922	0.95078	0.89765	0.10235

For example, the second stage analyses will take place when approximately 1546 patients have been enrolled and the study would be stopped for efficacy if the 90-day absolute mortality difference is less than -0.044. This corresponds to a one-sided p-value of 0.00479. If the alternative hypothesis is true, then the probability of stopping for efficacy at this stage is 0.529.

On the other hand, if the absolute mortality difference at the second stage is less than 0.01, corresponding to a one-sided p-value between 0.274 and 0.726, then the study may be stopped for futility. If the null hypothesis is true, then the probability of stopping for futility at this stage is 0.452.

Table 4 below shows the effect of changes in the power of the study as a function of the mortality rate on the treatment with the higher mortality. We calculated the power under two assumptions. The first is that the absolute difference in mortality rates was 4.5% and the second was a 30% relative difference. The second row of the table shows the current assumptions. Whether the absolute or the relative difference is used, the power remains above 85%.

Table 4. Sensitivity to Assumed Null Mortality

Null Mortality	Power at 4.5% Absolute Decrease in Mortality	Power at 30% Relative Decrease in Mortality
17%	0.86	0.93
15% *	0.90	0.90
13%	0.94	0.85

*Assumption used in the CLOVERS Protocol

9.2 Power Calculation for 28-day Organ Support Free Days

We also note that CLOVERS is powered to detect meaningful differences in important secondary outcomes. For example, we believe that organ failure free days to day 28 (e.g. not intubated, nor receiving renal replacement therapy, and not on vasopressors after a 48-hour period of protocol washout) is a relevant and meaningful outcome. In fact, since this is a study where one must select an approach that will resemble one of the strategies (e.g. this is a test of existing therapies, not of a novel therapy that would require adoption) a meaningful difference in organ failure free days would be a meaningful study result that would alter treatment practices.

To demonstrate the power for organ failure free days – we use published data from the PROMISE trial (which reported organ failure free days). PROMISE reported organ failure free days to day 28 in usual care (mean +/- standard deviation) for cardiovascular (20.6 +/- 11.9), respiratory (19.8 +/- 12.0), and renal (20.6 +/- 11.9). We assume that organ failure free days (combining all three organ systems) would be largely determined by the worst of the three components. Since these components are all quite similar, we use a standard deviation of 12 organ failure free days for sample size calculations. Consistent with the FACTT trial, we identify 3 organ failure free days as clinically significant. Using a two-side alpha of 0.05 we obtain 90% power to detect a true mean difference as outlined in the table below:

Difference in Organ Failure Free Days	Total Patients
4	382
3	**676**
2	1516

9.3 Effect of Change in Fluid Protocol on Outcome

The initial two-liter fluid infusion in the liberal fluid treatment group was modified to a one-liter fluid infusion followed by an optional additional liter at the treating physician's discretion. To understand the potential impact of this change in the liberal fluid treatment strategy on the primary outcome we will do an interaction analysis which will be presented as shown in the following table.

Table 5: All-Cause Mortality Prior to Discharge Home Before Day 90
Stratified by Liberal Fluid Treatment Epoch

Epoch	Liberal Fluid Group	Restrictive Fluid Group	Difference (95% CI)	P-value
Two-Liter Fluid Infusion Epoch	0.xxx±0.xxx	0.xxx±0.xxx	0.xxx (0.xxx, 0.xxx)	0.xxx
One-Liter Fluid Infusion Epoch	0.xxx±0.xxx	0.xxx±0.xxx	0.xxx (0.xxx, 0.xxx)	0.xxx
Interaction			0.xxx (0.xxx, 0.xxx)	0.xxx

The primary outcome analysis will be still based on a two-way comparison of all participants randomized to liberal fluid and all those randomized to restrictive fluid unstratified by the two liberal fluid treatment epochs as shown in the following table.

Table 6: All-Cause Mortality Prior to Discharge Home Before Day 90

Liberal Fluid Group	Restrictive Fluid Group	Difference (95% CI)	P-value
0.xxx±0.xxx	0.xxx±0.xxx	0.xxx (0.xxx, 0.xxx)	0.xxx

Interactions between the liberal and restrictive treatment groups and the two liberal fluid treatment epochs for study process metrics, such as intervention period fluid and vasopressor use, and selected secondary outcomes may also be reported as in Table 5 above.

10. Data Collection and Monitoring

Data Collection: The research coordinators will transfer data to the Clinical Coordinating Center on a prescribed basis through a secure web-based data collection program.

Investigators will use these reports to identify aspects of protocol management that can be improved at their Centers. The on-target performances of all centers will also be included, allowing investigators at each center to know how their center is performing relative to other PETAL Centers. On-target performances will be discussed during regular meetings of the Steering Committee. The Institutional Support Committee will provide advice and assistance to Centers that are not performing up to expectations. On-target data for the specific variables according to study group will be included in the primary reports of the results of the individual trials.

Site Monitoring: Data quality will be reviewed remotely using front end range and logic checks at the time of data entry and back-end monitoring of data using SAS reports. Additionally, Clinical Center on site visits will be performed on a regular basis by the Clinical Coordinating Center to ensure that all regulatory requirements are being met and to monitor data quality. Patient records and case report forms will be examined on a spot check basis to evaluate the accuracy of the data entered into the database and monitor for protocol compliance.

11. Risk Assessment

This study involves randomization to early restrictive fluids and early vasopressors versus liberal fluids with rescue vasopressor use for the first 24 hours.

11.1 Potential Risks to Subjects

Risk of Fluid Administration: Patients in the liberal fluid protocol may receive additional intravenous fluids. This carries the potential risk of fluid overload, including acute congestive heart failure, breathing difficulties, and increased peripheral edema.

Risk of Vasopressor Administration: Patients in the restrictive protocol may receive early or additional vasopressors based on the treatment assignment. The potential risks of early vasopressors include cardiac ischemia, cardiac dysrhythmias, bowel ischemia, or limb ischemia.

Risks of Blood Draws: All patients will have blood drawn for research purposes. Many patients will have invasive lines placed for clinical purposes, where the risk of blood draws are extremely low, as blood can usually be easily obtained from these lines. In cases where an invasive line is not present, the risks of drawing blood are uncommon and include bleeding and bruising. Commonly, drawing blood is painful, and rarely, drawing blood can lead to infections at the site of the blood draw.

Risk of Line Placement: Patients with hypotension will often have central venous access placed to increase venous access in the anticipation of the need for reliable and increased access for fluid, medication, and vasopressor administration. However, if restoration of blood pressure occurs without needing vasopressor medications, clinicians may decide to not place central venous access. Additionally, clinicians may opt to use peripheral venous access to administer vasopressors. The restrictive fluids protocol is intended to facilitate an increase in the utilization of vasopressors; thus, this practice may lead to an increase in the placement of central venous catheters. The decision to place a central venous line will be left to the treating and/or study clinician. It is possible that additional central venous catheters will be placed in the fluid restrictive group. The risks of central venous access include infection, pneumothorax (punctured lung), and vessel injury, inclusive of inadvertent arterial cannulation.

Peripheral Vasopressor Utilization: Peripheral vasopressor administration is permitted in this protocol. The risk of peripheral vasopressors utilization is extravasation and soft-tissue toxicity/injury if extravasation occurs.

11.2 Risk of Death

It is possible that one treatment arm may lead to more deaths; mortality will be monitored during the course of the study.

11.3 Minimization of Risk

Federal regulations at 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. There are several elements of study design inherent in the present protocol that meets this human subject protection requirement. The DSMB will be reviewing data as outlined above and will examine not only efficacy but safety (inclusive of mortality) and will reserve the right to halt the study at any time.

11.4 Potential Benefits

Study subjects may or may not receive any direct benefits from their participation in this study. It is unclear which type of fluid strategy provides optimal benefit. Thus, it is possible that were the restrictive or liberal arm shown to be superior, then patients in that arm may receive benefit. However, the optimal strategy is undefined at this point.

11.5 Risks in Relation to Anticipated Benefits

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits.

12. Human Subjects

Each study participant or a LAR must sign and date an informed consent form. Institutional review board approval will be required before any subject is entered into the study. PETAL will use a central IRB.

12.1. Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The EDs, ICUs, and other acute care areas of PETAL sites will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests or procedures will be performed as part of the screening process. If any subjects meet criteria for study enrollment, then the attending physician will be asked for permission to approach the patient or his/her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

12.2. Justification for Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of a type of treatment for patients with sepsis induced hypotension. Due to the nature of sepsis induced hypotension, the vast majority of these patients will have impaired decision-making capabilities. This study cannot be conducted if limited to enrolling only those subjects with retained decision-making capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

12.3. Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each prospective subject or the subject's LAR. The one obtaining consent is responsible for ensuring that the patient and/or LAR understands the risks and benefits of participating in the study, and answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the LAR's willingness to permit the subject's continued participation in the trial. The consenter will make every effort to minimize coercion. All study participants or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the LAR in simple terms before the patient is entered into the study, and to document that the LAR is satisfied with his or her understanding of the risks and

benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each patient or LAR. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures including administration of study agent.

12.3.1 Process of Obtaining Informed Consent

Informed consent will be obtained from the patient or from a surrogate decision maker if the patient lacks decision-making capacity.

In some instances, bringing a paper consent form and pen to the bedside of a patient with known or suspected COVID-19 and then taking these out of the room would violate infection control principles and policies. Given that many of the potential CLOVERS patients will not yet have been ruled out for COVID-19 at the time of consent, the use of "no-touch" consent methods will be allowed. Additionally, the electronic consent platform facilitates documentation of informed consent from legal authorized representatives who are not present in the hospital at the time that the LAR is approached for informed consent.

Below, we outline three examples of no-touch consent procedures that may be used: (a) a paper-based approach (method 1); (b) a second paper-based approach (method 2); and (c) an electronic/e-consent approach

a) Paper-based approach method 1

1. The informed consent document is delivered to the patient or LAR.
    a. If the patient or LAR is on-site, the informed consent document many be delivered to the patient or LAR either by research staff or by clinical staff
    b. If the LAR is off-site, the informed consent document may be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy)
2. Research staff discuss the informed consent document with the patient or LAR either in-person or by telephone or videophone. *This step confirms subject/LAR identity*.
3. If the patient or LAR decides to consent to participate, the patient or LAR signs and dates the paper copy of the informed consent document.
4. A photograph is taken of the signature page of the informed consent document and uploaded into the electronic database (e.g. REDCap).
    a. If using the patient's device (such as a patient's personal cellular phone), a survey link can be sent to their device to allow direct upload of the image into the electronic database (e.g. REDCap).
    b. If using a staff device, it must be approved to store PHI by the local institution. In that case, research personnel can take a photograph of the signature page of the informed consent document either directly or through the window or glass door leading into the patient's room. The photograph can then be uploaded into the electronic database. If a staff device is taken into the patient's room to take a photograph it must be able to be disinfected according to local institutional practices.

5. Research staff (and witness if applicable based on local requirements) provide signatures within the electronic database (e.g. REDCap) confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

b) Paper-based approach method 2

A photograph of the signed ICF can be transmitted to trial staff.

1. An unsigned ICF is provided to the patient by a person who has entered the room.
2. The investigator/designee arranges a telephone call or videoconference call with the patient (and, if desired and feasible, additional individuals requested by the patient [e.g., next of kin]).
3. To ensure the patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:
    a) Identification of who is on the call.
    b) Review of the ICF with the patient by the investigator/designee and response to any questions the patient may have.
    c) Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the ICF that is in their possession.
4. The patient (or an individual in the room) takes a photograph of the signed and dated ICF and sends it to the investigator/designee.
5. Research staff and LAR/patient provide signatures confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent documents for research records.

c) Electronic/e-consent approach

1. The electronic informed consent document is opened on a research device or a link for the electronic informed consent document is sent to the patient's or LAR's device.
2. Research staff discuss the informed consent document with the patient or LAR either in person or by telephone or videophone. This step confirms subject/LAR identity.
3. If the patient or LAR decides to consent to participate the patient or LAR signs the electronic informed consent document. This signature may be either:
    a. an actual signature (often tracing a finger on the screen) OR
    b. a username and password specific to the individual signing
4. Research staff and witness (if required by institutional standards) provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.

If a hospital device is provided to facilitate electronic or paper-based consent, that device will be disinfected according to institutional protocols and removed by research staff or clinical staff during the next entry into the patient's room.

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

The information for the informed consent discussion will be provided in a formal document (or electronic equivalent) that has been approved by the IRB and in a language comprehensible to the potential participant, using an interpreter if necessary. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient does not speak English, a short-form consent and qualified interpreter will be employed, using similar "no-touch" principles. Use of an interpreter and the interpreter's identity will be documented on the electronic consent.

12.4. Continuing Consent

Subjects for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in the hospital, will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent will be obtained

12.5. Withdrawal of Consent

Patients or the LAR may withdraw or be withdrawn (by the LAR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been explicitly withdrawn. If a patient or LAR requests termination of study procedures during the treatment period, the procedures will be stopped but the patient will continue to be followed up as part of the trial. If a patient or LAR withdraws consent during trial treatment, the study procedures will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or LAR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be assumed unless explicitly withdrawn.

12.6. Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol will often have limitations of decision-making abilities due to their critical illness. Hence, some patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the potential subject's legally authorized representative (LAR).

Regarding proxy consent, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a legally authorized representative (LAR) as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for subject participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the PETAL central IRB.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee (NBAC)), an investigator should accept a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place [28]. Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study [29].

12.7. Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that person with diminished autonomy are entitled to protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents greater than minimal risks. Commentators and research ethics commissions have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits ***similar*** to that available in the clinical setting [30]. Several U.S. task forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment." [31]. Finally, NBAC stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that "the potential subject's LAR gives permission…" [28]

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is ***similar*** to that available in the clinical setting, with the exception of the additional blood draws.

12.8. Additional Safeguards for Vulnerable Subjects

The present research will involve subjects who might be vulnerable to coercion or undue influence. As required in 45CFR46.111 (b), we recommend that sites utilize additional safeguards to protect the rights and welfare of these subjects. Such safeguards might include, but are not limited to: a) assessment of the potential subject's capacity to provide informed consent, b) the availability of the LAR to monitor the subject's subsequent participation and withdrawal from the study; c) augmented consent processes. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

12.9. Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all laboratory specimens, evaluation forms, and reports will be identified only by a coded number. The coded number will be generated by a computer, and only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained inside a locked office. Study information will not be released without the written permission of the patient, except as necessary for monitoring by the National Heart, Lung, and Blood Institute, and the PETAL Clinical Coordinating Center.

13. Adverse Events

13.1 Safety Monitoring

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. The Investigators will determine daily if any adverse events occur during the period from enrollment through **study day 6** (five days after completion of the study fluid protocol) or Hospital discharge, whichever occurs first.

The following adverse events will be collected in the adverse event case report forms:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study procedures or of uncertain relationship (Appendix G)

A clinical trial adverse event is any untoward medical event associated with study procedures, whether or not it is considered related to the study procedures.

After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the CCC their assessment of the potential relatedness of each adverse event to protocol procedure via electronic data entry. Investigators will assess if there is a reasonable possibility that the study procedure caused the event, based on the criteria outlined in Appendix G. Investigators will also

consider if the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant medications.

Determining whether a treatment is causally related to the development of increased oxygen requirements is a challenge, as it is difficult for a clinician to reliably discern hydrostatic from non-hydrostatic pulmonary edema. Furthermore, increased hypoxia and/or need for additional respiratory support may be due to disease progression (eg early phases of ARDS) or a fluid bolus and this is also difficult to discern. We will not consider the study endpoints of use of high-flow nasal cannula, non-invasive ventilation, or endotracheal intubation as AEs unless the events are judged by the investigator to be related to study procedures (see Appendix G2).

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

13.2 Serious Adverse Events

Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event after consent, but prior to randomization or starting study procedures, the event will NOT be collected. Study site personnel must alert the CCC of any **serious and study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix G for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs)

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Deaths
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization

As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- Persistent or significant disability/incapacity

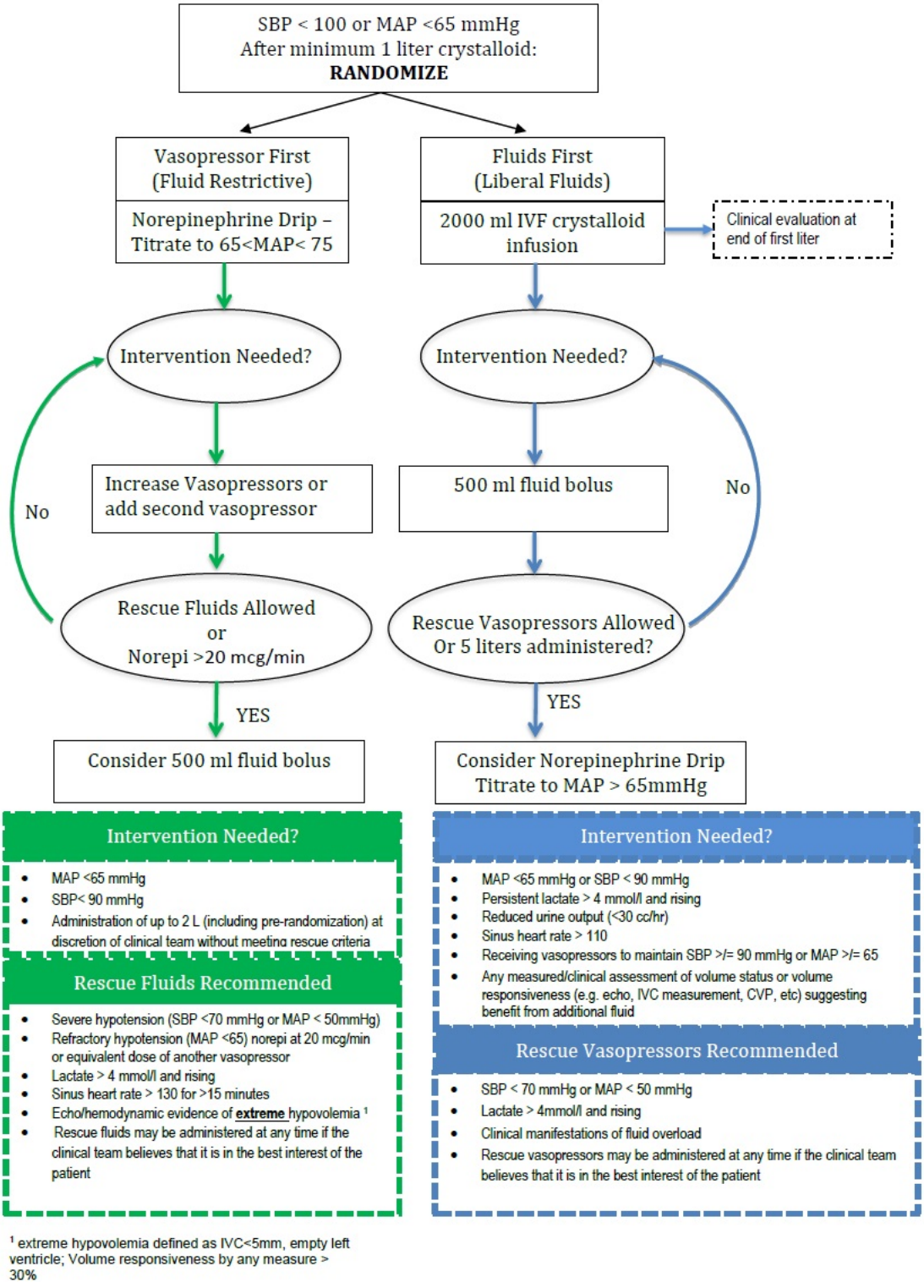
As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events will be collected during the first **6 study days** or until ICU discharge, whichever occurs first, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

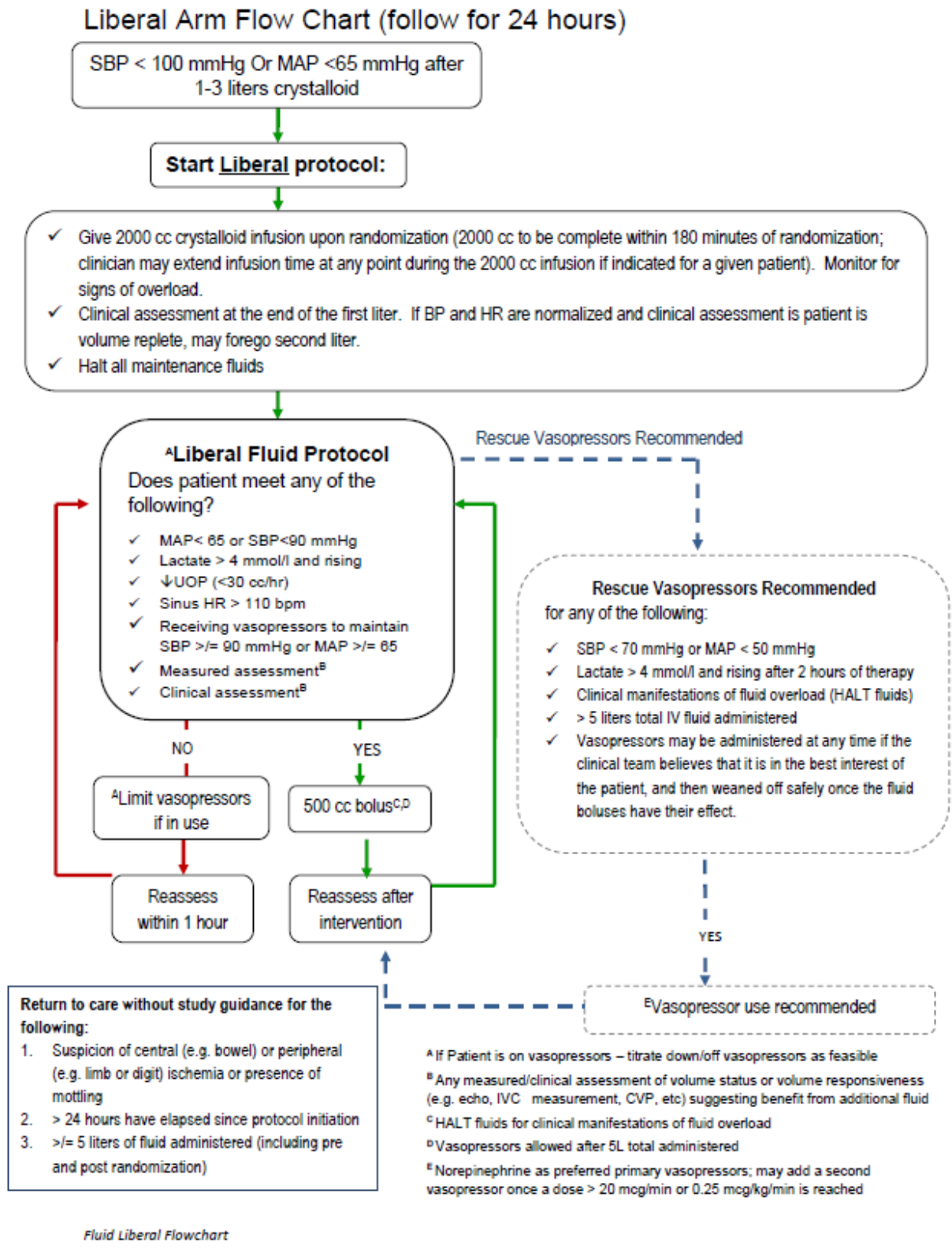
Appendices

A. Protocol Schema



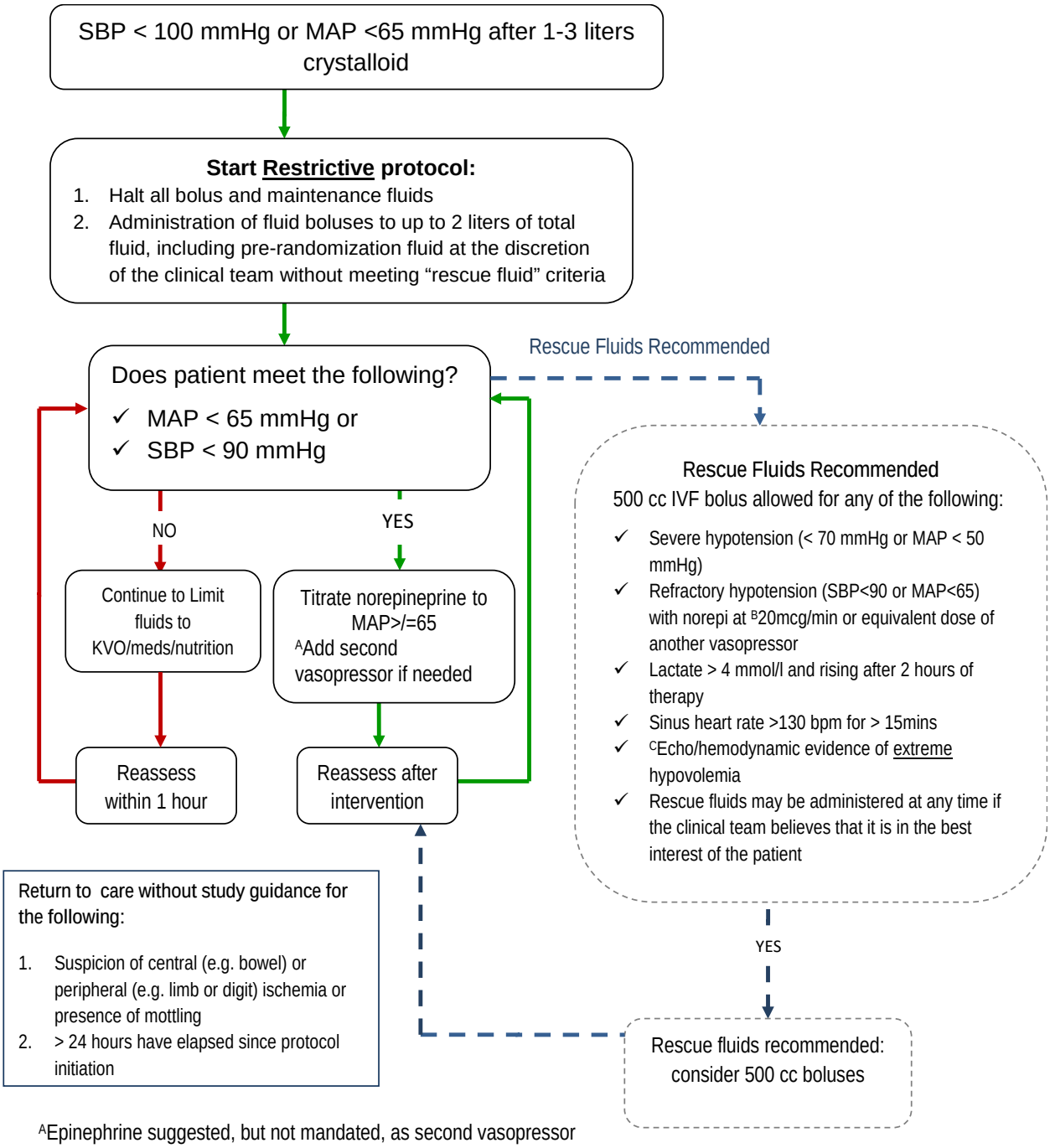
[1] extreme hypovolemia defined as IVC<5mm, empty left ventricle; Volume responsiveness by any measure > 30%

A.1 Liberal Protocol (follow for 24 hours)



Fluid Liberal Flowchart

A.2 Restrictive Protocol (follow for 24 hours)



[A]Epinephrine suggested, but not mandated, as second vasopressor

[B] Norepinephrine 20mcg/min or 0.25 mcg/kg/min

[C] Defined as: maximal IVC diameter < 5mm; or Empty left ventricle on echo (e.g. left-ventricular end-diastolic area index < 5.5 cm^2/m^2 BSA) or Substantial volume responsiveness defined as stroke volume increase > 30% in response to a passive leg raise, fluid challenge, or positive pressure breaths

B. Data and Safety Monitoring Board

The principal role of the DSMB is to assure the safety of patients in the CLOVERS trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the NHLBI with respect to:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

Two interim analyses will be conducted at approximately 33% and 66% target enrollment accrual.

The NHLBI PETAL Network DSMB is appointed by the Director, NHLBI and makes recommendations to the NHLBI Director. The DSMB reviews all protocols for safety following review by an independent NHLBI Protocol Review Committee. The DSMB will consist of members with expertise in acute lung injury, emergency medicine, biostatistics, ethics, and clinical trials. An NHLBI staff member not associated with PETAL will serve as Executive Secretary. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The Principal Investigator and the Medical Monitor of the CCC will be responsible for the preparation of all DSMB and adverse event reports and may review unblinded data. The DSMB will develop a charter and review the protocol and sample consent form during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the CCC. When appropriate, conference calls may be held in place of face-to-face meetings. Recommendations to end, modify, or continue the trial will be prepared by the DSMB executive secretary for review by Director, NHLBI. Recommendations for major changes, such as stopping, will be reviewed by the NHLBI Director and communicated immediately. Other recommendations will be reviewed by the NHLBI director and distributed in writing to the CCC, which will distribute to the PETAL steering committee with instructions for reporting to local IRBs when appropriate.

Details of the NHLBI policies regarding DSMBs can be found at the following URL:
http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm

The PETAL Network Steering Committee is comprised of the Principal Investigators and Co-investigators of all the Clinical sites, the CCC, and the NHLBI Project Officer who represents the NHLBI. All sites have two votes and the CCC has one.

C. SOFA Scoring System

Variables	SOFA Score				
	0	1	2	3	4
Coagulation **Platelets x 10^3/µL**	>150	</=150	</=100	</=50	</=20
Liver **Bilirubin, mg/dL**	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>11.9
Cardiovascular **Hypotension**	No hypotension	Mean arterial pressure <70 mmHg	Dop</=5 or dob (any dose) ‡	Dop >5, epi</=0.1, or norepi </=0.1‡	Dop >15, epi >0.1, or norepi >0.1‡
Renal **Creatinine, mg/dL** **or urine output, ml/d**	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>4.9 or <200

*Norepiindicates norepinephrine; Dob, dobutamine; Dop, dopamine, Epi, epinephrine.
†Values are with respiratory support.
‡Adrenergic agents administered for at least one hour (doses given are in µg/kg/min)

We define a clinically significant organ failure as a SOFA score 2 or more points higher than baseline.

D. Ventilator Weaning

Commencement of weaning

Patients will be assessed for the following weaning readiness criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures may be delayed for up to six hours. Patients can be assessed for weaning readiness criteria twice a day.

1. At least 12 hours since enrollment in the trial.
2. $FiO_2 \leq 0.40$ and PEEP ≤ 8 cm
3. Values of both PEEP and $FiO_2 \leq$ values from previous day (comparing Reference Measurement values, section 6.3).

Spontaneous breathing trial (SBT) procedure and assessment for unassisted breathing

If criteria 1-4 above are met, first the neuromuscular blocking agent will need to be discontinued if the medication is still being infused. When the neuromuscular blocking agent has worn off and the patient is having spontaneous respirations, then initiate a trial of up to 120 minutes of spontaneous breathing with $F_IO_2 \leq 0.5$ using any of the following approaches:

1. Pressure support < 5cm H_2O, PEEP $\leq$ 5cm H_2O
2. CPAP $\leq$ 5 cm H_2O
3. T-piece
4. Tracheostomy mask

Monitor for tolerance using the following:

1. $SpO_2 \geq 90\%$ and / or $PaO_2 \geq 60$ mmHg
2. Mean spontaneous tidal volume $\geq$ 4 ml / kg PBW (if measured)
3. Respiratory Rate $\leq$ 35 / min
4. pH $\geq$ 7.30 (if measured)
5. No respiratory distress (defined as 2 or more of the following):
    a. Heart rate ≥ 120% of the 0600 rate (≤ 5 min at > 120% may be tolerated)
    b. Marked use of accessory muscles
    c. Abdominal paradox
    d. Diaphoresis
    e. Marked subjective dyspnea.

If any of the goals 1-5 are not met, revert to previous ventilator settings or to PS + 10 cm H_2O with Positive End-expiratory Pressure and FiO_2 = previous settings and reassess for weaning the next morning.

The clinical team may decide to change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

Decision to remove ventilatory support

For intubated patients, if tolerance criteria for spontaneous breathing trial (1-5 above) are met for at least 30 minutes, the clinical team may decide to extubate. However, the spontaneous breathing trial can continue for up to120 minutes if tolerance remains in question. If any of criteria 1-5 are not met during unassisted breathing (or 120 minutes has passed without clear tolerance), then the ventilator settings that were in use before the attempt to wean will be restored and the patient will be reassessed for weaning (see section D.2) the following day.

Definition of unassisted breathing

a) Extubated with face mask, nasal prong oxygen, or room air, OR
b) T-tube breathing, OR
c) Tracheostomy mask breathing, OR
d) CPAP $\leq$ 5 without PS or IMV assistance
e) Use of CPAP or BIPAP solely for sleep apnea management
f) Use of a high flow oxygen system

E. Vasopressor Weaning

1. When MAP > 65 mmHg on a stable dose of vasopressor, begin reduction of the vasopressor by greater than or equal to 25% of the stabilizing dose at intervals of less than or equal to 4 hours to maintain MAP greater than or equal to 65 mmHg.
2. Dopamine is considered “discontinued" for vasopressor use and cell assignment when it is weaned to less than or equal to 5 mcg/kg/min, but should continue to be weaned per protocol.

Norepinephrine Equivalents:

- norepinephrine 1 mcg/min
- phenylephrine 2.5 mcg/min
- epinephrine 1 mcg/min
- vasopressin at any dose

F. Time Events Schedule

Measurement/Event	Baseline	(0-6 hrs)	(6-24 hrs)	1	2	3	4	5	6	7	28	90
Demographics, History and Physical	X											
Vital Signs	X				X							
Vasopressor use	X	X	X	X	X	X						
Fluid Administration	X	X	X									
O2, non-invasive and invasive ventilation		X	X									
Daily Fluid Balance (intake and output)				X	X	X	X	X	X	X		
Charlson Score	X											
GCS	X			X	X	X						
Laboratory/microbiology results	A			A	A	A						
Diuretic use				X	X	X	X	X	X	X		
ARDS assessment	X			X	X	X	X	X	X	X		
Plasma Collection	X			X		X						
DNA/RNA	X			X		X						
Plasma for IL-6 and banking	X			X		X						
Disposition											X	
Ventilator, Vasopressor, Renal replacement therapy use											X	
Assessment of infection source											X	
Vital Status											X	X

X=Required
A=When available

G. Adverse Event Reporting and Unanticipated Events

As noted in section 11.2, investigators will report all adverse events that are serious and study procedure related (or of uncertain relatedness) to the CCC within 24 hours. The CCC will then notify the NHLBI and Central Institutional Review Board (cIRB)

The Medical Monitor at the CCC will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study procedure, as outlined in 21 CFR 312.32**(a)**(1)I, and below. The Medical Monitor will also determine if the event is unexpected. An adverse is considered "unexpected" if it is not listed in the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by the study procedure, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The CCC will report all unexpected deaths, serious and treatment related adverse events, and SUSARs to the DSMB, NHLBI, and cIRB within 7 days after receipt of the report from a clinical site. A written report will be sent to the NHLBI, DSMB and the cIRB within 15 calendar days. The DSMB will also review all adverse events and clinical outcomes during scheduled interim analyses. If the DSMB determines that the overall rate of adverse events is higher in one fluid protocol group, the cIRB will be notified within 15 days of this determination. The CCC will distribute the written summary of the DSMB's periodic review of adverse events to the cIRB in accordance with NIH guidelines (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

G1. Unanticipated problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

G2. Determining relationship of adverse events to procedures

Investigators will be asked to grade the strength of the relationship of an adverse event to study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.

- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.

- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.

- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
  .
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

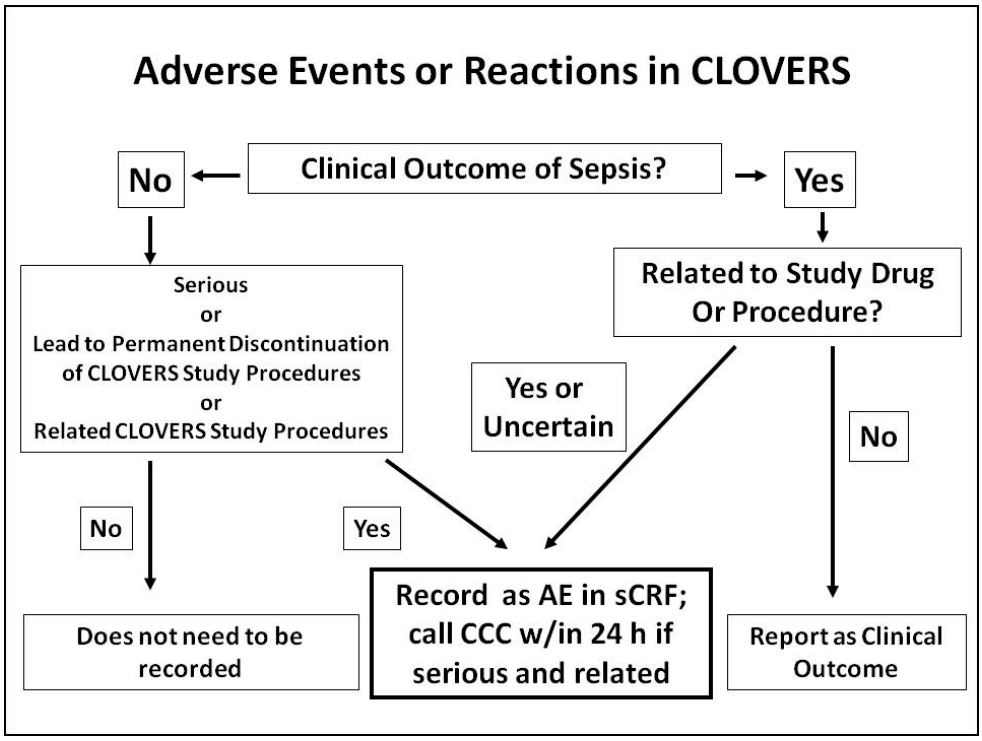
G3. Clinical outcomes that may be exempt from adverse event reporting

Study-specific clinical outcomes of sepsis, as outlined in Sections 3.8.1 and 3.8.2 (Primary and Secondary Outcomes) and Section 6.3 (Assessments During the Study) are exempt from adverse event reporting unless the investigator deems the event to be related to the study procedures (or of uncertain relationship) or if the event leads to discontinuation of study procedures. The following are examples of events that will be considered study specific clinical outcomes

- Death not related to the study procedures.
- Cardiovascular events: need for vasoactive drugs or fluids for hypotension or hypotension, Supraventricular/ventricular tachycardia (SVT) or new onset atrial fibrillation (AF). The occurrence of one or more episodes (sustained for more than 1 minute for SVT and AF) during the hospital stay will be recorded.
- Respiratory events: decreased PaO_2/FiO_2, hypoxia, worsening acute respiratory distress syndrome, or respiratory failure.
- Hepatic events: hepatic injury or liver dysfunction that leads to an increase from baseline in the serum level of bilirubin.
- Renal events: renal failure, renal insufficiency, or renal injury that leads to an increase from baseline in serum creatinine.
- Hematologic/coagulation events: coagulopathy, disseminated intravascular coagulation, thrombocytopenia, or thrombocytosis.

Note: Arrhythmias such as heart block or ventricular fibrillation are not considered study specific clinical outcomes and should be recorded as adverse events if they are serious events or are considered by the investigator to be related to study procedures.

G4. Decision tree for determining if an adverse event is reportable



Adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock**. N Engl J Med. 2012 May 31;366 (22):2055-64. Epub 2012 May 22. PubMed PMID: 226168**

H. Imputed P/F using SpO2 and FiO2

The equivalence table below determines the estimated P/F ratio from the FiO2 and SpO2. This data was generated by investigators at the University of Utah, on a cohort of critically ill patients with pneumonia [32-38].

SPO2	FiO2														
	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

For altitude adjustment, we will incorporate the practice from prior ARDS Network studies of using average ambient to sea level barometric pressure (for Utah, 0.86; for Denver, 0.84).

Additional requirements for the use of the S/F ratio include:

1. SpO_2 between 80-96%
2. SpO_2 should be measured at least 10 minutes after any change in FiO_2.
3. PEEP ≥ 5 cm H_2O
4. An adequate pulse oximeter waveform tracing

I. Language Cassettes Related to Provider Treatment Preference for the

CLOVERS Treatment Recommendations

Protocol elements

- **Subject recruitment plan and consent process:**

  Study staff will identify potential study participants, confirm that the attending physician agrees that the study patient and/or family can be approached for consent.

- **Study procedures – Screening for eligibility:**

  The attending physician of each patient eligible for inclusion will be contacted to confirm that the patient can be entered into the trial using a standardized script. The attending physician's decision will be documented in the case report forms as follows: Attending physician 1) agrees both CLOVERS arms are consistent with good medical care 2) Does not agree 3) Does not have the time to consider this question. Responses 2 or 3 will exclude the patient from participation

- **Patient recruitment - Standardized approach and script to be used to seek permission from attending physician to recruit a patient:**

  For each patient who is potentially eligible for the trial, the CLOVERS site investigator or coordinator will contact the patient's attending physician, with expertise in emergency or critical care medicine, and use the following script:

  > "Dr. <name>, I am calling to seek your permission to approach your patient, <name>, for
  > consent to participate in the CLOVERS trial. This is an NIH-funded trial that enrolls patients with early septic shock who have received one to three liters of fluid. I am required to ask you if both of the CLOVERS treatment recommendations are consistent with good medical care for your patient.
  >
  > According to the protocol, those randomized to the restrictive arm will receive a vasopressor (we recommend norepinephrine) if your patient is still hypotensive after randomization. Additional fluids are recommended if the norepinephrine dose exceeds 20 mcg/min, is ineffective (rising lactate, refractory hypotension, ischemia or mottling) or poorly tolerated (heart rate over 130). Those assigned to the liberal arm will receive a 2 liter infusion of crystalloid (we recommend lactated ringers or Plasmalyte) over up to 3 hours if still hypotensive after randomization and as tolerated. Additional 500 ml boluses are recommended for a systolic blood pressure < 90, oliguria, sinus tachycardia over 110, or indications of fluid responsiveness. Vasopressors are recommended for persistent hypotension (SBP < 70), lactic acidosis, or fluid overload. In both arms, fluids or vasopressors can be used at any time if you feel they are in the best interest of the patient. Patients can be withdrawn from the protocol if clinical circumstances change and adherence to the protocol places the patient at risk.
  >
  > We want to confirm that <name> is an appropriate candidate for the CLOVERS trial; and that in your clinical judgement both the restrictive and liberal fluid arms

are consistent with good medical care for this patient and that you acknowledge that fluids or vasopressors can be used at any time if you feel they are in the best interest of the patient."

This first two paragraphs will be used the initial time the trial team contacts the physician but could be skipped if the physician is already familiar with the protocol. The third paragraph will be stated when contacting an attending physician for any potential patient whether or not the physician has been contacted by the study team in the past. Patients will only be approached for consent if their physician confirms his/her belief that either management strategy is appropriate, per the third paragraph.

Exposure of attending and nursing staff to CLOVERS protocol training in both the Emergency Departments and Intensive Care Units will be documented in the study binder at each CLOVERS hospital.

J. SHAMROC Study Protocol

Title: SHAMROC: Sepsis-induced Hypotension: Assessing effect of Method of Resuscitation On patient-Centered outcomes

STATEMENT OF HYPOTHESIS AND SPECIFIC AIMS

Optimal resuscitation strategies for patients with sepsis-induced hypotension have been debated for decades. Critical questions are (a) whether to rely primarily on intravenous fluids (versus vasopressors), (b) how to optimally titrate the volume of fluid administered, and (c) whether vasopressors should be started earlier to spare the patient from large volumes of fluid. These key questions are relevant to hundreds of thousands of critically ill patients every year. Cross-national practices vary widely. Because individual clinicians hold strong opinions on the matter, observational studies remain hopelessly confounded by indication. Only randomization can persuasively disentangle the effects of strategies favoring fluids versus vasopressors.

The Crystalloids Liberal Or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial is a large (n=2,320) nationwide multi-center randomized clinical trial by the NHLBI-sponsored PETAL network to test whether an early “wet” fluid-intensive/pressor-restrictive strategy improves 90-day in-hospital mortality in patients with sepsis-induced hypotension, compared to an early “dry” fluid-restrictive/pressor-intensive strategy. CLOVERS presents a unique and fleeting opportunity to definitively measure patient-centered outcomes caused by markedly different initial resuscitation strategies. CLOVERS will enroll over 3 years, starting March 2018.

The pragmatic CLOVERS design focuses on hospital outcomes. Thus, CLOVERS will not address key patient-centered controversies that are prominent in the literature:

Cognitive Impairment: An ancillary study of the NHLBI-funded Fluid and Catheter Treatment Trial (FACTT) showed that randomization to a dry strategy in patients with ARDS was associated with impaired memory, verbal fluency, and executive functioning—with a quadrupling of the odds of cognitive impairment (71% cognitively impaired vs 38%, OR: 4.0 (95% CI: 1.5–10.6)) despite identical in-hospital mortality—but, in a sample of just 75 survivors of ARDS, not all with sepsis.

Physical Disability: Observational analyses suggest that net fluid balance at ICU discharge is a determinant of subsequent mobility and ability to return home. Simplistically, edema increases the work required to move and contributes to stiffness, pain, and impaired balance. More subtly, aggressive fluid resuscitation may lengthen mechanical ventilation due to pulmonary edema, and the ventilator itself may be a driver of systemic inflammation. This combination of inactivity, inflammation, and risk for complications could lead to prolonged institutional care and subsequent disability. Existing data are inconclusive.

Importantly, the prior literature suggests that a wet strategy may be superior for some outcomes (*eg*, better cognitive function), but a dry strategy may be superior for other outcomes (*eg*, decreasing disability). Patients and clinicians want individualized information about cognitive and disability outcomes to make treatment choices. But—because wet versus dry fluid strategies may affect these outcomes differently—we must measure these outcomes directly to

interpret the CLOVERS RCT. **Sepsis-induced Hypotension: Assessing effect of Method of Resuscitation On patient Centered outcomes (SHAMROC)** study prospectively measures outcomes in an estimated 1,420 surviving CLOVERS participants not already profoundly cognitively impaired or disabled prior to randomization.

AIM 1: Test the hypothesis that randomization to dry resuscitation for sepsis-induced hypotension results in worse cognitive impairment at 6 and 12 months compared to wet resuscitation. Survivors will undergo treatment-blinded centralized telephone assessment of overall cognitive function (Montreal Cognitive Assessment, the MoCA-Blind) and specifically executive function (Hayling Sentence Completion Test).

Aim 1b: Test the hypotheses that differences are mediated by (a) days of mechanical ventilation, (b) severity of hypoxemia, or (c) rates of acute renal failure.

AIM 2: Test the hypothesis that randomization to wet resuscitation for sepsis-induced hypotension results in worse physical disability at 6 and 12 months compared to dry resuscitation. Survivors will undergo treatment-blinded centralized telephone assessment of overall physical disability (activities and instrumental activities of daily living (I/ADLs), using the functional limitations survey from the Health and Retirement Study) and of mobility and strength (10 Items from the NIH PROMIS Mobility Bank).

Aim 2b: Test the hypotheses that differences are mediated by (a) net fluid balance, (b) days of mechanical ventilation, or (c) rates of acute renal failure.

AIM 3: Test the hypothesis that the net benefit of randomization to wet versus dry resuscitation on cognitive impairment and on physical disability will vary across individual patient's baseline risk for these outcomes. We will develop *de novo* risk scores in this trial for the specific purposes of both qualitatively and quantitatively testing for clinically meaningful differences in responses to wet versus dry resuscitation.

BACKGROUND

It is important for interventional trials to look for outcomes beyond mortality. Decades ago, Fried and colleagues demonstrated that patients and families value functional independence and cognitive outcomes more highly than survival-at-any-cost.(3) However, most studies of critical care interventions are designed only to look at mortality outcomes, including CLOVERS.

There are compelling arguments why resuscitation strategy might causally impact long-term outcomes other than mortality. Mikkelsen and colleagues conducted a secondary analysis on a subgroup of the ARDS Network FACTT investigation of fluid management after resolution of shock which suggested that a fluid restrictive strategy may be causally associated with cognitive impairment, particularly in domains of executive function, verbal fluency and memory.(1, 2) This study, along with additional observational work, raises the concern that the fluid restrictive arm of CLOVERS could place patients at risk for impaired cognitive function.

However, the converse could also be true—perhaps a fluid liberal resuscitation strategy is associated with poorer outcomes. There are compelling observational data directly and

indirectly suggesting that volume overload is associated with physical functional impairment. For example, significant volume overload at ICU discharge in patients with septic shock is independently associated with inability to walk at the time of hospital discharge, and lower likelihood of discharging home (as opposed to continued post-hospital institutional care). (4) It is clear that fluid liberal strategies are associated with prolonged mechanical ventilation, which, in turn, is strongly associated with weakness and poorer functional outcome at hospital discharge and after.(1, 5).

In sum, observational data are inadequate in unraveling the relationship between resuscitation strategy and long-term outcomes, since indication bias and unmeasured confounders risk causal interpretation of potential associations. As such, CLOVERS represents a once-in-a-lifetime opportunity to address key knowledge gaps, including: does initial resuscitation strategy impact cognitive outcomes and functional disability, and are there identifiable effect modifiers of this relationship?

PRELIMINARY DATA

Cognitive impairment and disability are common after sepsis, even among patients without impairment in the year prior to sepsis hospitalization. (6) Simple instruments that can be reliably administered over the telephone can detect these impairments, both with patient and proxy participation. For example, in a subgroup of 269 patients in the Health and Retirement Study who had no limitations on pre-sepsis assessment of Individual or Instrumental Activities of Daily Living, sepsis hospitalization was independently associated with 1.57 new limitations. Similarly, accounting for pre-sepsis cognitive baseline, sepsis hospitalization was associated with a tripled odds of moderate/severe cognitive impairment using a telephone-administered assessment.

Endpoints

There is one primary endpoint for Aim One: Cognitive Impairment as determined by MOCA-Blind administered at 6 and 12 months after CLOVERS enrollment (or proxy-assessed equivalent measure).

There is one primary endpoint for Aim Two: Disability as determined by ADL/iADL, assessed via either patient or proxy.

Study Design

Inclusion/Exclusion Criteria

Inclusion Criterion: Enrolled in CLOVERS

Exclusions:

1. Severe premorbid cognitive impairment or disability (by screening AD8 and ADL/iADL at CLOVERS enrollment)
2. Patient neither fluent in English nor Spanish
3. Patient is homeless

Study Population & Enrollment

SHAMROC is an ancillary study to the parent RCT of CLOVERS that will determine the effect of randomization arm (resuscitation strategy) on cognitive impairment and disability measured 6 and 12 months after enrollment, using an intention to treat analysis for Aims 1 and 2. Aim 3 is an exploratory analysis evaluating potential effect modifiers in the relationship between fluid strategy and primary outcomes.

Risks

Steps have been taken to minimize the risks of this study. Even so, potential risks may include the following: patients may experience various emotions when responding to the interview questions. However, they may choose to skip any interview question they feel uncomfortable answering.

Another risk is the possible loss of confidentiality of the interview responses. We believe that risk of a breach of confidentiality is low. Throughout the study, IRB and HIPAA guidelines will be followed to ensure the privacy and integrity of the information we collect.

There may be other risks that are unforeseeable at this time.

Data Collection

Three categories of data will be needed for SHAMROC.

1. Data collected for CLOVERS: Most needed data reflecting demographics, comorbidities, acute illness variables, data describing hospital course, and hospital outcomes will be obtained as part of the CLOVERS protocol. SHAMROC will obtain these data from the CCC. Additionally, we will need randomization assignments (after trial unblinding). Hospital-course data will be obtained after CLOVERS is complete. Demographic, hospital outcome, destination of discharge, and contact information will be transferred in realtime, as these data will be required for post-hospital follow-up.
2. Data added to baseline assessment: In order to determine eligibility for SHAMROC, we will need to collect 5 additional data elements at the time of CLOVERS enrollment. These data points are encompassed in less than 25 simple questions which add 5-10 minutes of time to CLOVERS and will be compensated by SHAMROC. These data points include:
    a. Baseline cognitive screen (using the Alzheimer's Disease 8, AD8) via an eight question survey designed for proxies
    b. Baseline disability (using the Individual and Instrumental Activities of Daily Living instruments, the same as is used in ROSE) via a thirteen question survey validated in proxies
    c. Current living situation (using the single item, same as in ROSE)
    d. Contact information, using the same data collection sheet as ROSE
    e. Language spoken by the patient
3. Data will be collected during 6- and 12-month interviews: All eligible and surviving patients will be contacted by the University of Michigan, University of Washington or

Oregon Health and Science University (OHSU will only contact patients enrolled at their site), for participation in telephone assessment of cognitive function and disability. Subjects (or proxies if subjects unable to participate) will complete 7 instruments, for an estimated total call duration of 20-30 minutes. Participants will be compensated for their time. Surveys will be conducted in English or Spanish, and include:

a. Cognitive assessment: Montreal Cognitive Assessment-Blind (if patient participating) or AD8 (if proxy participating) (7-9) (10, 11) (12)
b. Executive function assessment: Hayling Sentence Completion Test (patient only, no Spanish)
c. EQ-5D-5L
d. Disability assessment: ADL/iADL instrument (patient or proxy) (13) (14) (15)
e. Mobility assessment: PROMIS Mobility short form (patient or proxy) (16)
f. Current living situation
g. Recent healthcare use

Each participant will receive a $10 token of appreciation after each 6- or 12-month interview, in the form of a gift card to a national chain of stores. In addition, each participant will be mailed a reminder postcard prior to the 6- and 12-month interviews. Each participant will receive a $5 token of appreciation for returning the postcard with updated contact information.

Because of the importance of having an excellent response rate, we have a protocol to avert refusals, specifically an increase from the original $10 to $20. This increased amount is based on prior studies as well as advice with personnel at the University of Michigan Health and Retirement Study (HRS), launched in 1992 and funded by the National Institute on Aging and the Social Security Administration. Their procedures have been well vetted, and are still in use in the 2014 fielding of the HRS. Research has shown that refusal conversions increase cooperation rates significantly for all incentive levels.

Interviewers will be trained on how to avert refusals during the initial participant contact by addressing any concerns that the respondent may have. After gauging participation rates over the course of the study, study staff may find it necessary to offer an incentive of $20 during the initial contact. This will take place if the participant is hesitant during the initial contact in hopes that participation rates will increase. In the event that a respondent does not wish to participate in subsequent surveys after having completed their first survey, we will then offer an additional incentive of $10 for a total of $20. Once a participant is offered the higher incentive, they will receive that amount for each of the remainder of surveys that they complete.

In no case will more than $20 be offered to avoid any potential for coercion, although examples of much higher incentives certainly exist in the literature. For example, Turnbull et al recently published a study with incentives up to $50, and Robinson et al's recent systematic review noted studies with incentives up to $160.

The interviewers have demonstrated their excellence with telephone administration of surveys and the central assessment of all long-term outcomes in the ROSE study (FUNCTION, led by Drs. Jack Iwashyna and Mic Couper). Final survey completion rates were 88.5%, 85.5%, and 84.8% at 3-, 6-, and 12-months, respectively.

Statistical Considerations

Sample size: CLOVERS has an anticipated sample size of 2320. We anticipate that no more than 20% will be ineligible due to severe pre-existing cognitive impairment or disability, languages other than English or Spanish (since CLOVERS consent is only being conducted in these two languages), or lack of telephone or permanent address, leaving 1856 potentially eligible for SHAMROC analyses. As described in analytic plan below, note that patients who die before follow-up are retained in the analytic cohort.

Primary Analysis for Aim 1: "Does randomization to different resuscitation strategies cause a difference in cognitive function, unbiased by differences in mortality-based selection?" Differential mortality can lead to misleading analyses of the impact of treatment on outcomes. This has been termed "selection bias"(86), "informative censoring," or "censoring of the extreme phenotype".(87) There is no universally accepted solution to this problem. We propose the approach of Permutt and Li of the Office of Biostatistics at the U.S. Food and Drug Administration and also endorsed by recent NHLBI-sponsored review.(88) This approach recognizes that death is extremely poor cognitive function, just not assessed on the same numeric scale as the MoCA-Blind or HSCT. This approach will be used for the primary analysis using MoCA-Blind, and an executive function-specific secondary analysis using HSCT.

The method of Permutt and Li calculates an empirical cumulative distribution function (ECDF) for the fraction of patients with cognitive impairment, considering all possible dichotomizations of the cognition scores (including informative non-response due to poor cognition and death as the most extreme forms of poor cognition).

Measuring Potential Mediators in SHAMROC. All will be collected as part of the CLOVERS CRF.
Days of mechanical ventilation in the first 28 after randomization will be measured, as will the development of ARDS in first 7 days. (Aims 1 & 2)
Severity of hypoxemia will be measured as the lowest routinely obtained pulse oximetry saturation on the daily logs, obtained during the first 7 days in the ICU. (Aim 1)
Renal failure will be defined by the KDIGO staging system (serum creatinine criteria only (89)) between baseline and 7 days to assess for *de novo* or worsening acute kidney injury. As treatment assignment could impact urine output, we will use only the creatinine criteria.(90) Patients on chronic dialysis will be ineligible for this analysis. (Aims 1 & 2)
Net fluid balance will be defined as a proportion change in body weight compared to admission, as in (18). (Aim 2)

Permutt and Li thereby avoid loss of information and the controversy associated with selecting a single cut-point (*ie*, with the Rankin scale), while giving an interpretable summary statistic. Permutt and Li demonstrate that the mean outcome scores among the better performing patients from each study arm ("trimmed means") are efficient statistics for reporting the between-group differences using the intention to treat principle. They recommend trimming each trial arm equally, just above the expected overall rate of death and non-response. In SHAMROC, 33% of each study arm will be "trimmed."

Under this trimming, the test statistic has a straightforward interpretation: “How large of a difference in average cognitive function is caused by randomization to wet versus dry resuscitation, measured in the better-off ⅔ of patients?” Permutt and Li developed a permutation test for the confidence interval for this test statistic under no assumptions other than randomization, which is particularly appealing given the often-skewed distributions of cognitive function scores. We will report both the test statistic (with 95% CI) and graphically present the ECDF curve for each randomized group to summarize all data.

If necessary due to missing data in the electronic case report form (CRF)—which is not expected—we will use a Bayesian implementation of the model to impute missing values nested within sites, using a Gibbs sampler to impute from the posterior of the missing data given observed data.(91-95)

Mediation Analysis for Mechanism.

We hypothesize that differences in cognitive outcome between wet and dry resuscitation may stem from differences in rates of intervening organ dysfunctions and hypoxia. Respiratory dysfunction may harm the brain by either hypoxemia, exposure to deliriogenic medications and practices,(96) or systemic effects of ventilator-induced lung injury.(97) Renal dysfunction may harm the brain by escalating inflammation (98) and multiple organ dysfunction, progression to chronic kidney disease,(99) uremia, or exposure to dialysis (“dialysis brain” or “hemodialysis fatigue syndrome” (100)). Hypoxemia was a major independent predictor of poor outcome in ACOS.(11, 101, 102)

To test mediation if there is a difference between treatment groups, we will generalize the primary analysis. Permutt and Li demonstrate that analysis of covariance (ANCOVA) can be used to estimate the trimmed mean test statistic, adjusting for a potential mediator. This is repeated on each of the permuted datasets to develop confidence intervals. This allows us to assess—one-by-one for each potential mediator—the magnitude of the difference in average cognitive function between wet and dry treatment arms explained by each mediator.

Analysis for Aim 2: “Does randomization to different resuscitation strategies cause a difference in physical disability, unbiased by differences in mortality-based selection?”
Paralleling our approach in Aim 1, we will use the method of Permutt and Li to assess: “How large of a difference in average physical disability is caused by randomization to wet versus dry resuscitation, measured in the better-off two-thirds of patients?” Death will be considered as an extreme form of physical disability, and permutation tests will be used to calculate a confidence interval for this test statistic under no assumptions other than randomization. We will report both the test statistic (95% CI) and graphically present the ECDF curves by randomized group.

Mediation Analysis for Mechanism. Similar to effects on cognitive impairment, we hypothesize that initial resuscitation strategy may affect disability outcomes through a number of key pathways. We will focus on respiratory failure, renal failure, and persistent hypervolemia as potential mediating factors. Respiratory failure is consistently associated with post-ICU disability, with likely contributions from immobility, increased days of delirium/coma due to sedation, higher levels of inflammation, and longer duration of hospitalization. Loss of muscle

mass, for example, is accelerated in patients with respiratory failure and shock(115). It is possible that acute respiratory failure and mechanical ventilation will be more common in the wet resuscitation strategy arm because of increased pulmonary edema. Renal failure may differ between study arms and is another factor frequently associated with physical impairment after critical illness, with increased incidence of muscle loss and weakness.(115, 116) The 2 resuscitation strategies will have significant differences in fluid balance, particularly among patients with shock persisting past the first 4 hours.

Paralleling Aim 1, we will use Permutt and Li's ANCOVA to answer: "How large of a difference in average physical disability is caused by randomization to wet versus dry resuscitation, measured in the better-off ⅔ of patients, controlling for differences in the hypothesized mediator?" We will also report the fractional reduction of the unadjusted effect that is associated with each hypothesized mediator.

Analysis for Aim 3: We hypothesize that the net benefit of wet versus dry resuscitation on cognitive impairment and physical disability will vary across individual patients, based on a patient's baseline risk for these outcomes. To test whether the magnitude of this variation is clinically meaningful across patients, we will complete pre-specified sub-group analyses in which patients are stratified into tertiles of risk for cognitive impairment (and separately, by tertiles of risk for physical disability). In addition, we will assess for HTE directly by testing for an interaction between treatment assignment and baseline risk for predicting 6-month outcome within a regression model. These two complimentary approaches to assessing and presenting HTE (risk-based subgroup analysis and an interaction term) are recommended as "best practices" for the testing and reporting HTE.(20)

References

1. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, et al. Comparison of two fluid-management strategies in acute lung injury. The New England journal of medicine. 2006;354(24):2564-75. doi: 10.1056/NEJMoa062200. PubMed PMID: 16714767.

2. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. American journal of respiratory and critical care medicine. 2012;185(12):1307-15. doi: 10.1164/rccm.201111-2025OC. PubMed PMID: 22492988; PubMed Central PMCID: PMC3381234.

3. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. The New England journal of medicine. 2002;346(14):1061-6. doi: 10.1056/NEJMsa012528. PubMed PMID: 11932474.

4. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL. Volume Overload: Prevalence, Risk Factors, and Functional Outcome in Survivors of Septic Shock. Annals of the American Thoracic Society. 2015;12(12):1837-44. doi: 10.1513/AnnalsATS.201504-187OC.

5. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, et al. The RECOVER Program: Disability Risk Groups and 1-Year Outcome after 7 or More Days of Mechanical Ventilation. American journal of respiratory and critical care medicine. 2016;194(7):831-44. doi: 10.1164/rccm.201512-2343OC. PubMed PMID: 26974173.

6. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. Jama. 2010;304(16):1787-94. PubMed PMID: 20978258.

7. Hobson J. The Montreal Cognitive Assessment (MoCA). Occup Med (Lond). 2015;65(9):764-5. doi: 10.1093/occmed/kqv078. PubMed PMID: 26644445.

8. Nasreddine ZS, Phillips N, Chertkow H. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. Neurology. 2012;78(10):765-6; author reply 6. doi: 10.1212/01.wnl.0000413072.54070.a3. PubMed PMID: 22391608.

9. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x. PubMed PMID: 15817019.

10. Christie JD, Biester RC, Taichman DB, Shull WH, Jr., Hansen-Flaschen J, Shea JA, et al. Formation and validation of a telephone battery to assess cognitive function in acute respiratory distress syndrome survivors. J Crit Care. 2006;21(2):125-32. doi: 10.1016/j.jcrc.2005.11.004. PubMed PMID: 16769455.

11. Pendlebury ST, Welch SJ, Cuthbertson FC, Mariz J, Mehta Z, Rothwell PM. Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone interview of cognitive status and telephone Montreal Cognitive Assessment versus face-to-face Montreal Cognitive Assessment and neuropsychological battery. Stroke. 2013;44(1):227-9. doi: 10.1161/STROKEAHA.112.673384. PubMed PMID: 23138443; PubMed Central PMCID: PMCPMC5593099.

12. Wallace RB, Herzog AR, Weir DR, Ofstedal MB, Langa KM, Fisher GG, et al. Documentation of Cognitive Functioning Measures in the Health and Retirement Study. Ann Arbor, MI: Survey Research Center, University of Michigan, 2005.

13. Organization WH. The International Classification of Functioning, Disability and Health (ICF) Geneva: WHO; 2001. Available from: http://www.who.int/classifications/icf/en/.

14. Wallace RB, Herzog AR, Ofstedal MB, Fonda SJ, Steffick D, Langa KM, et al. Documentation of Physical Functioning Measured in the Heath and Retirement Study and the Asset and Health Dynamics among the Oldest Old Study Ann Arbor, MI: Survey Research Center, University of Michigan, 2004.

15. Ahasic AM, Van Ness PH, Murphy TE, Araujo KL, Pisani MA. Functional status after critical illness: agreement between patient and proxy assessments. Age Ageing. 2015;44(3):506-10. doi: 10.1093/ageing/afu163. PubMed PMID: 25324334; PubMed Central PMCID: PMCPMC4411220.

16. Hays RD, Spritzer KL, Amtmann D, Lai JS, Dewitt EM, Rothrock N, et al. Upper-extremity and mobility subdomains from the Patient-Reported Outcomes Measurement Information System (PROMIS) adult physical functioning item bank. Arch Phys Med Rehabil. 2013;94(11):2291-6. doi: 10.1016/j.apmr.2013.05.014. PubMed PMID: 23751290; PubMed Central PMCID: PMCPMC3812258.

17. Permutt T, Li F. Trimmed means for symptom trials with dropouts. Pharm Stat. 2017;16(1):20-8. doi: 10.1002/pst.1768. PubMed PMID: 27523396.

18. Colantuoni E, Scharfstein DO, Wang C, Hashem MD, Leroux A, Needham DM, et al. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. BMJ. 2018;360:j5748. doi: 10.1136/bmj.j5748. PubMed PMID: 29298779.

19. Cohen J. Statistical Power Analysis for the Behavioral Sciences 2nd ed. New York: Lawrence Erlbaum Associates; 1988.

20. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials. 2010;11:85. doi: 10.1186/1745-6215-11-85. PubMed PMID: 20704705; PubMed Central PMCID: PMC2928211.

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486-552. doi:10.1097/CCM.0000000000002255.

2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77. doi:10.1056/NEJMoa010307.

3. Investigators P, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683-93. doi:10.1056/NEJMoa1401602.

4. Investigators A, Group ACT, Peake SL, Delaney A, Bailey M, Bellomo R et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496-506. doi:10.1056/NEJMoa1404380.

5. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301-11. doi:10.1056/NEJMoa1500896.

6. Lilly CM. The ProCESS trial--a new era of sepsis management. N Engl J Med. 2014;370(18):1750-1. doi:10.1056/NEJMe1402564.

7. SJ L, K R, JG P, O G, G L, R K. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: A retrospective cohort study. Chest. 2014;146:908-15.

8. Nguyen HB, Jaehne AK, Jayaprakash N, Semler MW, Hegab S, Yataco AC et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care. 2016;20(1):160. doi:10.1186/s13054-016-1288-3.

9. FORUM NQ. NQF #0500 Severe Sepsis and Septic Shock: Management Bundle. In: NQF #0500 Severe Sepsis and Septic Shock: Management Bundle. http://www.qualityforum.org/NQF_Revises_Sepsis_Measure.aspx.

10. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695-705. doi:10.1007/s00134-016-4500-7.

11. Marik PE. Iatrogenic salt water drowning and the hazards of a high central venous pressure. Ann Intensive Care. 2014;4:21. doi:10.1186/s13613-014-0021-0.

12. (CMS) CfMaMS. CMS to Improve Quality of Care during Hospital Inpatient Stays. In: (CMS) CfMaMS, editor.2014.

13. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779-89. doi:10.1056/NEJMoa0907118.

14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637. doi:10.1097/CCM.0b013e31827e83af.

15. Lewis RJ. Disassembling goal-directed therapy for sepsis: a first step. JAMA. 2010;303(8):777-9. doi:10.1001/jama.2010.203.
16. Jones AE. Unbundling early sepsis resuscitation. Ann Emerg Med. 2014;63(6):654-5. doi:10.1016/j.annemergmed.2013.10.034.

17. JA M, RS H, RM W, al e. Rosen's Emergency Medicine: Concepts and Clinical Practice. Philadelphia: 2006.

18. Cardenas-Garcia J, Schaub KF, Belchikov YG, Narasimhan M, Koenig SJ, Mayo PH. Safety of peripheral intravenous administration of vasoactive medication. J Hosp Med. 2015;10(9):581-5. doi:10.1002/jhm.2394.

19. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care. 2015;30(3):653 e9-17. doi:10.1016/j.jcrc.2015.01.014.

20. Kelm DJ, Perrin JT, Cartin-Ceba R, Gajic O, Schenck L, Kennedy CC. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock. 2015;43(1):68-73. doi:10.1097/SHK.0000000000000268.

21. Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care. 2010;14(4):R142. doi:10.1186/cc9207.

22. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med. 2016;42(12):1935-47. doi:10.1007/s00134-015-4134-1.

23. Dong ZZ, Fang Q, Zheng X, Shi H. Passive leg raising as an indicator of fluid responsiveness in patients with severe sepsis. World J Emerg Med. 2012;3(3):191-6. doi:10.5847/wjem.j.1920-8642.2012.03.006.

24. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. Crit Care. 2014;18(6):696. doi:10.1186/s13054-014-0696-5.

25. Legrand M, Dupuis C, Simon C, Gayat E, Mateo J, Lukaszewicz AC et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care. 2013;17(6):R278. doi:10.1186/cc13133.

26. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483-95. doi:10.1056/NEJMoa1101549.

27. LAN KKG, DEMETS DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.

28. National Bioethics Advisory Commitee (NBAC). Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity. Rockville: U.S. Government Printing Office; 1998.

29. Office of Human Research Protections (OHRP). Compliance Determination Letters. 2002. http://ohrp.osophs.dhhs.gov/detrm_letrs/.

30. Dresser R. Research Involving Persons with Mental Disabilities: A Review of Policy Issues and Proposals. National Bioethics Advisory Commission. Rockville: U.S. Government Printing Office; 1999. p. 5-28.

31. American College of Physicians. Cognitively Impaired Subjects. Ann Int Med. 1989;111:843-8.

32. Ellis RK. Determination of PO2 from saturation. Journal of applied physiology. 1989;67(2):902.

33. Rice T, Wheeler A, Bernard G, Hayden D, Schoenfeld D, Ware L et al. Comparison of the Sp02/FI02 Ratio and the PaO 2/FI02 in Patients with Acute Lung Injury or ARDS. Chest. 2007;132(2):410-7.

34. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. J Hosp Med. 2013;8(2):83-90. doi:10.1002/jhm.1996.

35. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. Journal of applied physiology: respiratory, environmental and exercise physiology. 1979;46(3):599-602.

36. Dean NC, Jones JP, Aronsky D, Brown S, Vines CG, Jones BE et al. Hospital admission decision for patients with community-acquired pneumonia: variability among physicians in an emergency department. Ann Emerg Med. 2012;59(1):35-41. doi:10.1016/j.annemergmed.2011.07.032.

37. Brown SM, Jones BE, Jephson AR, Dean NC, Infectious Disease Society of America/American Thoracic S. Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. Crit Care Med. 2009;37(12):3010-6. doi:10.1097/CCM.0b013e3181b030d9.

38. Van de Louw A, Cracco C, Cerf C, Harf A, Duvaldestin P, Lemaire F et al. Accuracy of pulse oximetry in the intensive care unit. Intensive Care Med. 2001;27(10):1606-13. doi:10.1007/s001340101064.