Acetaminophen in Sepsis: Targeted Therapy to Enhance Recovery (ASTER)

ASTER: A PETAL Network Multi-Center Phase 2b Randomized Double-Blinded Placebo-Controlled Trial originally designed to evaluate Two Different Pharmacologic Therapies (Intravenous Vitamin C or Intravenous Acetaminophen). The Vitamin C arm was stopped on June 15, 2022.

VERSION: 4.5 April 25, 2023

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Contents

Revisions to the Protocol

Protocol Version 4.5

Date: April 25, 2023

Substantive protocol changes in Version 4.5:

1. Updates to the Protocol Cover Page were made to match changes in the protocol committee members' list.

Protocol Version 4.4

Date: July 7, 2022

On June 15, 2022, the study was paused due to publication of the Lessening Organ dysfunction with Vitamin C [1] trial demonstrating that intravenous Vitamin C at the dose used in this study was unlikely to benefit a similar population of participants as enrolled in ASTER and may be harmful [1]In addition, the sample size was revised based on a new estimate of the standard deviation of the primary outcome (organ support free days; OSFDs) to support the feasibility of completing the trial while retaining 85% power to detect the originally postulated 2.5 OSFD day difference with acetaminophen. Lastly, certain aspects of the protocol including exclusions that were relevant only to the vitamin C arm were removed.

Substantive protocol changes in Version 4.4:

1. Removal of all language related to Vitamin C from the following sections:
    - 1. Abbreviations and Definitions
    - 2.1 Title
    - 2.2 Objective, 2.3 Hypotheses, 2.4 Study Design, 2.4.1 Treatment Arms, 2.4.2 Sample Size/Statistical Considerations (sample size changed from 900 to 450 and Acetaminophen/placebo arms changed from 300 to 225), 2.6 Exclusion Criteria (#7, 13, 14, and 21 removed), 2.7 Primary Efficacy Variable, 2.8 Secondary Clinical Efficacy Variables, and 2.10 Safety Variables
    - 3.1.2 Cell-free hemoglobin (CFH) and organ dysfunction in sepsis
    - Removal of section 3.2 Vitamin C: Preclinical and Clinical Data
    - 3.4 Summary
    - 4.1 Study Description, 4.2 Randomization, 4.3 Primary Efficacy Variable, 4.4 Secondary Clinical Efficacy Variables, and 4.5 Safety Variables
    - 5.3 Vitamin C Arm-Active and 5.4 Vitamin C-Placebo Arm sections removed and 5.1 Acetaminophen-Active, 5.2 Acetaminophen-Placebo Arm sections revised to "Acetaminophen Arm" and "Placebo Arm"
    - 6.3 Exclusion Criteria (#7, 13, 14, and 21 removed) and 6.4 Reasons for each of the exclusion criteria

- 6.5 Co-enrollment
- 6.7 Excluded Medications and 6.8 On-study Fever Management Recommendations
- Section 6.10 Blood Glucose Strategy for the Vitamin C-Active/Vitamin C-Placebo Arm removed
- 6.12 Criteria for Discontinuation or Withdrawal
- 7.5 90-day All-Cause Mortality
- 7.6 Sample Collection; Biological Endpoint Assays bullet
- 8.1 Primary Endpoint
- 8.2 Sample Size (stopping boundaries revised for sample size without Vitamin C arm and single placebo group)
- 8.3 Secondary endpoints (Renal calculi endpoint also removed)
- 8.5 Safety Endpoints
- 8.7 Interim Analysis (subject enrollment numbers changed from 450 to 218 in addition to removal of Vitamin C language, corresponding stopping boundaries updated, and paragraph after Table 3 removed)
- 9.0 Risk Assessment, 9.1 Potential Risks to Subjects, and 9.4 Potential Benefits
- 11.1.1 Safety Monitoring
- Appendix A. Schedule of Events: “or vitamin C” removed from non-study administration row and Assessment of kidney stones removed from Outcome data section.
- Appendix E. Adverse Event Reporting and Unanticipated Events

2. Revision of exclusion criterion #15 (Protocol Sections 2.6 and 6.3: Exclusion Criteria):
   - Current language: *Use of home oxygen for chronic cardiopulmonary disease*
   - Revised language: *Use of home oxygen > 3 liters/min nasal cannula for chronic cardiopulmonary disease*

Rationale for this change:

Exclusion modification:

- A modest requirement for home oxygen to treat cardiorespiratory disease could be reasonably described as chronic respiratory insufficiency, rather than chronic respiratory failure. Described this way, chronic respiratory insufficiency could be analogous to patients with chronic renal insufficiency manifesting as reduced GFR without a requirement for chronic dialysis. Patients with reduced GFR are eligible for ASTER, provided they meet other inclusion criteria.
- Based on the most recent ASTER monthly report (SeeTable 2), 120 participants have been excluded because of the use of home oxygen for chronic cardiopulmonary disease, 86 as the sole reason for exclusion, and 34

Table 2: Reasons for Exclusion

	# Sole Reason for Exclusion	# One of Many Reasons for Exclusion	# Total Patients with Exclusion
Use of home oxygen for chronic cardiopulmonary disease	58	27	85

as one of many reasons for exclusion. At actively screening sites, this is the number one reason to exclude a potential ASTER participant. If 86 additional participants had been included in the study as of May 2022, enrollment to-date would have been increased by 60-70%.
    - Interpretation of the study's primary efficacy variable, number of organ failure free days to day 28, would not be affected by modifying this exclusion. To meet the respiratory system component of the primary efficacy variable, the participant must require assisted ventilation for at least 1 day. Assisted ventilation is currently defined in the ASTER trial as any level of invasive or noninvasive ventilator support including continuous positive airway pressure of >5 cmH20, bilevel positive pressure ventilation, or invasive mechanical ventilation. Noninvasive ventilation solely for sleep disordered breathing and nasal high flow oxygen therapy are not considered "assisted ventilation" for this study.
    - Though patients with a home oxygen requirement may be more susceptible to acute respiratory failure, we anticipate randomization would obviate any arm-specific bias introduced by this increased susceptibility.
  - There is no biologic rationale for why a patient with underlying chronic respiratory insufficiency might not benefit from APAP
  - To aid the study team in interpreting participant eligibility, we will create a FAQ that helps clarify that if a participant meets inclusion criteria based on a 6L nasal cannula oxygen requirement, the infection (or presumed infection) should be the primary reason for an increase in oxygen needs from any baseline oxygen requirement.
3. Correction to study drug administration in the Schedule of Events (SOE) table: Administration of study drug was missing from the Baseline (Day 0) timepoint in the table. The SOE table in Appendix A has been corrected to reflect study drug administration of the first dose on Day 0 (within 4 hours of randomization).

Protocol Version 4.3

Date: November 30, 2021

Initial protocol

1. Abbreviations and Definitions

1.1 Abbreviations

ABG = Arterial Blood Gas

APAP = Acetaminophen

ALI = Acute Lung Injury

ALT = Alanine Aminotransferase

ARDS = Acute Respiratory Distress Syndrome

AST = Aspartate Aminotransferase

BIPAP = Bi-level Positive Airway Pressure

BMI = Body mass index

BP = Blood Pressure

CCC = Clinical Coordinating Center

CFH = Cell-free hemoglobin

CPAP = Continuous Positive Airway Pressure

CRF = Case Report Form

Day 0 = Day of Randomization

DSMB = Data and Safety Monitoring Board

ELISA = Enzyme-linked Immunosorbent Assay

ED = Emergency Department

F_2-IsoP = F_2-Isoprostanes

FDA = Food and Drug Administration

FiO_2 = Fraction of Inspired Oxygen

GCS = Glasgow Coma Scale

HFNO = High Flow Nasal Oxygen

HUVEC = Human Umbilical Vein Endothelial Cells

ICF = Informed Consent Form

ICU = Intensive Care Unit

IMV = Intermittent Mechanical Ventilation

IL-6 = Interleukin-6

IL-8 = Interleukin-8

IRB = Institutional Review Board

IV = Intravenous

LAR = Legally Authorized Representative

LPS = Lipopolysaccharide

MAP = Mean arterial blood pressure

MBW = Measured Body Weight

mL = Milliliter

mmHg = Millimeter of Mercury

NHLBI = National Heart Lung and Blood Institute

NIV = Non-invasive ventilation

NSAID = Nonsteroidal anti-inflammatory drug

PaO2 = Partial pressure of arterial oxygen

PBW = Predicted Body Weight

PEEP = Positive End-Expiratory Pressure

Pplat = Plateau pressure

PSV = Pressure Support Ventilation

POC = Point of Care

RALE = Radiographic Assessment of Lung Edema

RCT = Randomized Controlled Trial

RRT = Renal Replacement Therapy

SAE = Serious Adverse Event

SBP = Systolic Blood Pressure

SBT = Spontaneous Breathing Trial

SOFA = Sequential (Sepsis-related) Organ Failure Assessment

SpO2 = Oxygen Saturation by Pulse Oximetry

SUSAR = Suspected and Unexpected Serious Adverse Reaction

UAB = Unassisted Breathing

VFD = Ventilator-free Days

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: 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: Any level of invasive or noninvasive ventilator support including continuous positive airway pressure of >5 cmH20, bilevel positive pressure ventilation, or invasive mechanical ventilation. Noninvasive ventilation solely for sleep disordered breathing and nasal high flow oxygen therapy are not considered "assisted ventilation" for this study.

Baseline: Prior to randomization

Chronic Dialysis: Receipt of hemodialysis or peritoneal dialysis for renal failure prior to hospitalization. This does not include new renal replacement therapy or hemofiltration initiated within 36 hours of randomization.

Date of first Unassisted Breathing (UAB): Defined as the first day that the subject is on UAB from midnight to midnight. Example: if subject meets UAB at 1900 on 6/1/14, then the date of first UAB would be 6/2/14, as long as subject does not return to AB on 6/2/14.

Day zero: Defined as the day of randomization (until 23:59 of the study day).

Days Alive and Free of Organ Support: Days alive and free of assisted ventilation, vasopressors and new renal replacement therapy over 28 days

Extubation: Removal of an orotracheal or nasotracheal tube, or unassisted breathing with a tracheostomy

Fluid Bolus: 500 ml or more of isotonic crystalloid

High Flow Nasal Oxygen: Oxygen delivered by nasal cannula at a rate of at least 30 liters/min, using a system capable of delivering up to 100% humidified and heated oxygen at flow rates up to 60 liters per minute.

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

Invasive Mechanical Ventilation: Mechanical ventilation delivered through an endotracheal or tracheostomy tube.

Legally Authorized Representative: Any 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

Serious Adverse Event: Adverse events that are serious and have a reasonable possibility that the event was due to a study drug or procedure.

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

Study withdrawal: Defined as permanent withdrawal from study the before completion of study activities. This does not include those subjects who have completed the protocol procedures. If a patient or surrogate requests withdrawal from the study the investigator 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.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with 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, or room air, T-tube breathing, tracheostomy collar (mask) breathing, or CPAP ≤ 5 without PSV or IMV assistance, nasal high flow oxygen, or the use of noninvasive ventilation solely for sleep-disordered breathing. Assisted breathing is any level of ventilatory support at pressures higher than the unassisted breathing thresholds.

2. Trial Summary

2.1 Title

Acetaminophen and Ascorbate in **S**epsis: **T**argeted Therapy to **E**nhance **R**ecovery **(ASTER)**
ASTER is a platform originally designed to conduct two separate trials. In response to external trial results, enrollment in the Vitamin C arm of the trial was suspended on June 15, 2022. The Acetaminophen (APAP) arm of the trial was resized and will continue as described in this amended protocol.

2.2 Objective

Objective: To carry out one multi-center phase 2b randomized double-blinded placebo-controlled trial of one pharmacologic therapy. The trial will assess the efficacy of Acetaminophen (1 gram intravenously every 6 hours) in comparison to placebo for 120 hours in patients with sepsis who have evidence of either hemodynamic or respiratory organ failure. The placebo infusion (5% dextrose in water, D5W) will match the volume and storage temperatures of the acetaminophen (room temperature, dose adjusted for weight below 50 kg)

2.3 Hypothesis

Hypothesis: Acetaminophen (APAP) infusion will increase the days alive and free of organ support to day 28.

2.4 Study Design

Prospective multi-center phase 2b randomized placebo-controlled double-blinded interventional trial of intravenous Acetaminophen for patients with sepsis-induced hypotension or respiratory failure.

1. Enrollment Period: Approximately 15 months
2. Patient Population: Critically ill adults admitted or planned admission to the ICU with sepsis and either hemodynamic or respiratory organ failure. A maximum of 450 patients will be enrolled
3. Locations: Emergency Department and ICUs at hospitals participating in the NHLBI PETAL Network

2.4.1 Treatment Arms

Patients with sepsis and either hemodynamic or respiratory organ failure on enrollment will be randomized to one of two treatment arms in a 1:1 fashion. The two arms will be Acetaminophen and Placebo randomized 1:1.

1. Acetaminophen given intravenously at the dose of 1 gram (or 15 mg/kg if patient weighs < 50 kg) every six hours for 5 days (20 doses) ***OR***

2. Placebo (identical appearing 5% dextrose solution) infused every six hours for 5 days (20 doses)

NOTE: The volume of placebo infusions will be lower in patients <50kg and will be matched to Acetaminophen.

Patients, nurses, research staff, and physicians will be blinded to the treatment assignment. The time of randomization will represent time zero. Study drug will be started within 4 hours of randomization**.**

Duration	Timing of Dosing	Subsequent Dosing
Treatment will continue for **120 hours (20 doses**), or discharge from the intensive care unit, study withdrawal, or death, whichever comes first.	*First study drug dose* (APAP or placebo) will be considered "Dose 1" and will be administered within **4 hours of randomization**. Study drug will be infused over 30 minutes.	**Subsequent doses will be infused every six hours (+/- 1 hour) through 120 hours or 20 doses (whichever comes first).** If a dose cannot be administered within 3 hours of the scheduled time, the dose should be skipped. Any dose administered outside of the +/- 1 hour window or any dose that is skipped will trigger a protocol deviation

2. **Completion of study drug administration**: Study drug administration will occur for a total of 120 hours, unless one of the following occurs:
    1. Discharged from the study hospital
    2. Discharge from the ICU
    3. Withdrawal from the study
    4. Death
    5. New AST or ALT elevation ≥ 10 times the upper limit of normal -

2.4.2 Sample Size/Statistical Considerations:

With randomization of 450 total patients (225 Acetaminophen 225 placebo)we will have 85% power to detect a difference between groups of 2.5 days in the primary composite outcome of

days alive and free of organ support (dialysis, assisted ventilation, and vasopressors) to day 28. Patients will be analyzed on an intention-to-treat basis based on randomization assignment.

2.5 Inclusion Criteria

1. Age ≥ 18 years
2. Sepsis defined as:
   a. Clinical evidence of a known or suspected infection and orders written to administer antibiotics

   AND

   b. Hypotension as defined by the need for any vasopressor (and at least 1 liter of fluid already administered intravenously for resuscitation) **OR** respiratory failure defined by mechanical ventilation, BIPAP or CPAP at any level, or greater than or equal to 6 liters/minute of supplemental oxygen (criterion b must be present at the time of randomization)
3. Admitted (or intent to admit) to a study site ICU within 36 hours of presentation to the ED or any acute care hospital

2.6 Exclusion Criteria

1. No consent/inability to obtain consent from the participant or a legally authorized representative
2. Patient unable to be randomized within 36 hours of presentation to the ED or within 36 hours of presentation to any acute care hospital
3. Diagnosis of cirrhosis by medical chart review
4. Liver transplant recipient
5. AST or ALT greater than five times the upper limit of normal
6. Diagnosis of ongoing chronic alcohol use disorder/abuse by chart review; if medical record unclear, use Appendix F
7. Hypersensitivity to Acetaminophen
8. Patient, surrogate or physician not committed to full support (Exception: a patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest)
9. Home assisted ventilation (via tracheotomy or noninvasive) except for CPAP/BIPAP used only for sleep-disordered breathing
10. Chronic dialysis
11. Use of home oxygen > *3 liters/min nasal cannula* for chronic cardiopulmonary disease
12. Moribund patient not expected to survive 24 hours
13. Underlying malignancy or other condition with estimated life expectancy of less than 1 month

14. Pregnant woman, woman of childbearing potential without a documented negative urine or serum pregnancy test during the current hospitalization, or woman who is breast feeding
15. Prisoner
16. Treating team unwilling to enroll because of intended use of Acetaminophen

2.7 Primary Efficacy Variable

Primary efficacy variables will be evaluated comparing Acetaminophen vs. placebo The primary efficacy variable is days alive and free of organ support (dialysis, assisted ventilation, and vasopressors) to day 28.

Participants will need to be free of all three components (assisted ventilation, vasopressors, new renal replacement therapy) to qualify for a day alive and free from organ failures. A patient could be free of all organ failures from day 10 through day 22 and then die on day 22 and would receive 12 days of credit for this primary outcome. The components of this outcome (days free of assisted ventilation, vasopressors, and new renal replacement therapy in the overall cohort and in survivors, and 28-day hospital mortality) will also be reported as secondary outcomes (see below in 2.8).

2.8 Secondary Clinical Efficacy Variables

Secondary efficacy variables will be evaluated comparing Acetaminophen vs. placebo.

1. 28-day ventilator-free days
2. 28-day vasopressor-free days
3. 28-day new renal replacement-free days
4. 28-day hospital mortality
5. 28-day ICU free-days
6. 28-day hospital-free days to discharge home
7. 28-day duration of ICU stay in survivors and non-survivors
8. Initiation of assisted ventilation to day 28
9. Initiation of renal replacement therapy to day 28
10. Change in Sequential Organ Failure Assessment (SOFA) scores between enrollment and study day 7
11. 90-day hospital mortality (includes death at any healthcare facility that is not the equivalent of home for a patient)
12. Development of ARDS within 7 days of randomization
13. Change in serum creatinine from enrollment to discharge, death, initiation of dialysis or 28 days, whichever occurs first
14. Major Adverse Kidney Events at 28 days (MAKE28): persistent increase in serum creatinine by 200% from baseline, need for new renal replacement therapy, or death

15. Change in the Radiographic Assessment of Lung Edema (RALE) score from enrollment to study day 3 in patients who are receiving assisted ventilation or high flow nasal oxygen at baseline.
16. 90-day all-cause mortality

2.9 Safety Variables

The safety monitoring and analyses will be performed separately on the Acetaminophen and placebo arms (1 active to 1 placebo randomization ratio). The safety variables will include the following:

1. Hypersensitivity or rash
2. AST and ALT measured on study days 0, 2-5, and 7 (day 7 measurement can be ±1 day).
3. The plasma levels of Acetaminophen will be obtained as a trough level just prior to administration of a study dose on study day 2 (subject must have received at least 5 doses of study drug before the day 2 samples are obtained) for all patients. After the first 100 patients have been enrolled who have been randomized to the Acetaminophen arm, the trough levels will be reported to the DSMB to determine if they exceed the level of 20 micrograms/mL, the potential level for hepatotoxicity.
4. Administration of fluid bolus, new use of vasopressor, or increased dose of vasopressor within 120 minutes of study drug infusion.
5. Incidence of reported adverse events

2.10 Biological Endpoints

Change in plasma IL-6, angiopoietin-2, cell-free DNA, syndecan-1, and cell-free hemoglobin between enrollment (baseline) and Days 2 and 3.

3. Trial Description

3.1 Background

3.1.1 Background-Sepsis and sepsis-related organ dysfunction

Sepsis is a common condition with over 750,000 cases per year in the U.S. and an associated mortality of at least 18-38% [2, 3]. The primary cause of death in sepsis is organ dysfunction, including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and cardiovascular dysfunction. ARDS is a common complication of sepsis; in a large multicenter international study of ARDS, sepsis (pulmonary or extrapulmonary) was the most common cause of ARDS [4]. Mortality from sepsis-induced ARDS is higher than mortality from ARDS due to other causes [5]. AKI is also common in sepsis, occurring in greater than 50% of patients [6-8]; the range of morbidity associated with AKI is broad, including prolonged ICU length of stay, need for renal replacement therapy (RRT), and death. Furthermore, ARDS and AKI commonly occur together, suggesting overlapping pathophysiologic mechanisms. The development of AKI in patients with ARDS increases mortality [9]. However, despite the magnitude of this clinical problem, there are still no specific therapies for sepsis other than

antimicrobials, and no specific therapies that reduce the severity of sepsis-associated ARDS, AKI or cardiovascular dysfunction [10].

3.1.2 Cell-free hemoglobin (CFH) and organ dysfunction in sepsis

Sepsis causes alterations in the red blood cell membrane that lead to release of CFH into the circulation due to membrane damage [11-13]. In an animal model of cecal-ligation and puncture induced sepsis, CFH can be measured in the plasma and levels of CFH are associated with mortality and worse renal function, an effect that is potentiated by deficiency of haptoglobin, hemopexin, or heme oxygenase-1[14]. In critically ill adults with sepsis, CFH is present in 80%-90% of patients, is associated with oxidative injury as measured by plasma F_2-isoprostanes (F_2-IsoP), and is independently associated with an increased risk of in-hospital mortality [15, 16] (**Figure 1**).

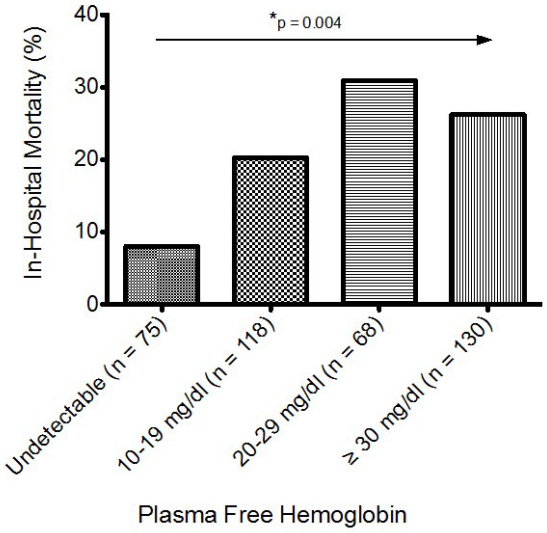


Figure 1. Plasma cell-free hemoglobin levels are significantly associated with in-hospital mortality in 391 critically ill patients with sepsis (14)

Mechanisms of toxicity of CFH in sepsis include the ability of CFH to scavenge nitric oxide, leading to vasoconstriction in various vascular beds [17-20], proinflammatory effects of CFH and its heme subunit [21-23] and the ability of CFH to undergo redox cycling, leading to oxidation of lipid membranes and release of F_2-IsoP [24, 25]; plasma levels of F_2-IsoP, are increased in patients with sepsis and are associated with renal, hepatic, and coagulation failure, and mortality [26]. This trial will test one agent, Acetaminophen, that can specifically target the injurious effects of CFH, present in the vast majority of patients with sepsis, to reduce organ dysfunction and affect clinical outcomes. To determine whether pre-enrollment point-of-care measurement of plasma CFH can be used for predictive enrichment in a future phase 3 trial of this agent, samples will be collected at enrollment in the current trial for post hoc measurement of plasma CFH to determine what level of pre-enrollment plasma CFH is optimal for predictive enrichment.

3.2 Acetaminophen—Preclinical and Clinical Data

The systemic inflammatory response to infection in sepsis creates an oxidative environment that has the potential of oxidizing the iron in CFH from the Ferrous (Fe 2+) to the ferryl (Fe 4+) state, creating an iron radical capable of organ injury [15, 25, 27]. Acetaminophen, at normal therapeutic concentrations, is a potent and specific inhibitor of hemoprotein-mediated lipid peroxidation owing to its ability to reduce the ferryl-protoporphyrin radical generated with release of hemoproteins into the circulation (**Figure 2**) [27, 28]. The hemoprotein reductant activity of Acetaminophen is independent of its other pharmacologic mechanisms, including prostaglandin H_2 synthetase and cyclooxygenase inhibition [28, 29]. In an experimental study in rats, Acetaminophen was highly effective in preventing oxidative damage and renal failure in the setting of myoglobinemia due to rhabdomyolysis [27]. In an observational study of patients with sepsis, receipt of Acetaminophen was associated with decreased F_2-IsoP levels and independently associated with decreased in-hospital mortality [15].

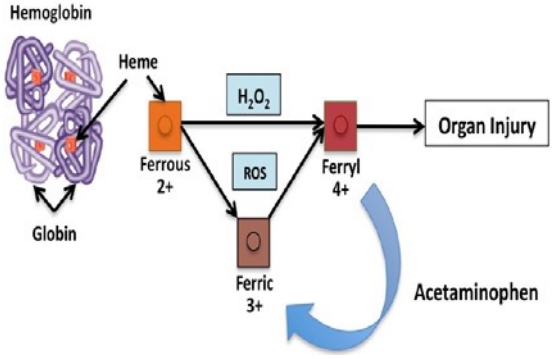


Figure 5. Release of cell free hemoglobin into an oxidizing environment as in sepsis, leads to formation of the highly reactive Fe4+ ferryl radical

In the isolated perfused human lung, addition of CFH to the perfusate causes acute lung injury manifested by an increase in lung vascular permeability and pulmonary edema formation as measured by lung weight gain and increased alveolar capillary barrier permeability to protein as measured by accumulation of Evans Blue labeled albumin in the airspaces of the lung. In this human lung preparation, addition of Acetaminophen to the perfusate blocked the effects of CFH on vascular permeability and pulmonary edema formation **(Figure 3)**.

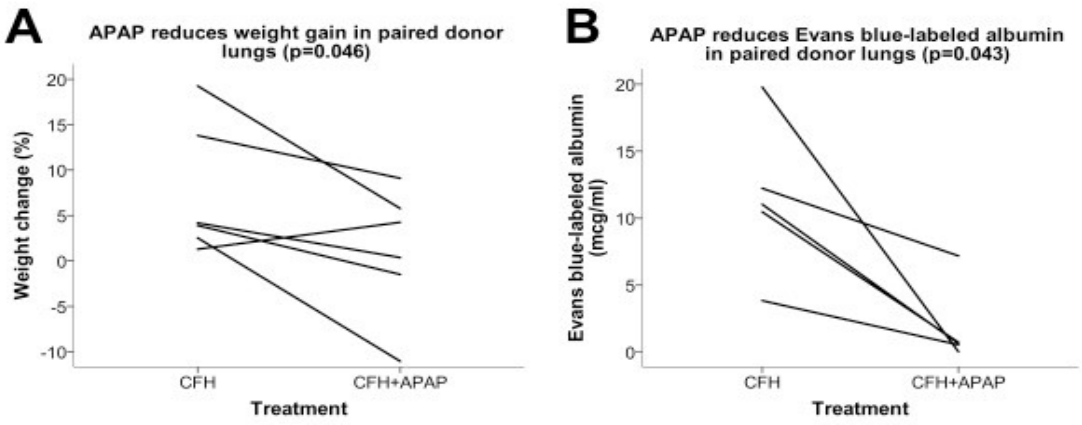


Figure 6. Addition of Acetaminophen (APAP) to the perfusate blocks the effects of CFH on pulmonary edema formation (panel A) and alveolar capillary barrier permeability (panel B) in paired isolated perfused human donor lungs.

The Ware group conducted a phase 2a, randomized, double blind, placebo-controlled pilot clinical trial of enteral Acetaminophen in 40 critically ill adults with severe sepsis [30] entitled the ACROSS I Trial (Acetaminophen for the Reduction of Oxidative injury in Severe Sepsis). Patients were enrolled within 24 hours of admission to the ICU. After enrollment, blood was drawn for measurement of plasma CFH to identify patients who may benefit from Acetaminophen therapy. Patients with undetectable CFH (<10 mg/dL) were not randomized, while patients with any amount of CFH (≥ 10 mg/dL) were randomized to enteral Acetaminophen at the dose of 1 gram enterally every 6 hours or placebo for 3 days. Notably, 91% of patients who met inclusion criteria for this trial had detectable CFH and thus were eligible for randomization. The primary endpoint was plasma F_2-IsoP on study day 3, with secondary endpoints of F_2-IsoP on study day 2 and serum creatinine on study day 3.
On study day 3, F_2-Isoprostanes were not significantly lower in the Acetaminophen group (30 pg/mL, IQR 24-41) compared with placebo (36 pg/mL, IQR 25-80, p = 0.35) although power was reduced at that timepoint due to patient dropout. However, F_2-Isoprostanes were significantly reduced on study day 2 in the Acetaminophen group (24 pg/mL, IQR 19 – 36) compared with placebo (36 pg/mL, IQR 23-55, p = 0.047). Creatinine on study day 3 was significantly lower in the Acetaminophen group (1.0 mg/dL, IQR 0.6–1.4) compared with placebo (1.3 mg/dL, IQR 0.83 – 2.0, p = 0.039). This difference persisted beyond study completion **(Figure 4A**). There was no statistically significant difference in hospital mortality (Acetaminophen 5.6% vs. placebo 18.2%, p = 0.355) although there was a trend for benefit (**Figure 4B**). There were no significant adverse events (AST or ALT >400, Acetaminophen 9.5% vs. placebo 4.3%, p = 0.599).

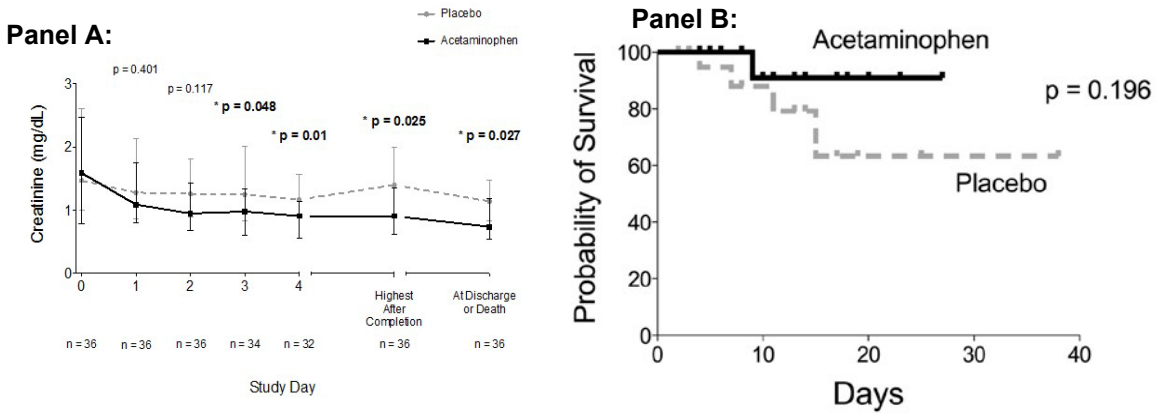


Figure 7, Panel A: Creatinine measured at enrollment, each study day, and after study completion in patients never requiring renal replacement therapy. **Panel B:** Hospital survival by treatment group.

Although the reduction in biomarkers of oxidative injury in the study was not consistent across all analyses, the biologic plausibility of benefit with Acetaminophen in patients with sepsis and detectable CFH, ease and safety of administration, consistent although non-significant improvement across all clinical outcomes, and the finding of improved renal function in sepsis warrants a larger Phase 2b trial in sepsis patients. A recent clinical trial of oral Acetaminophen in severe falciparum malaria also showed a reduction in creatinine in the treated arm with no adverse safety signal, further supporting the need for larger clinical trials [31]. A phase 3 trial of acetaminophen for treatment of severe falciparum malaria in the Democratic Republic of Congo (NCT04251351) began enrolling in December 2021.

Another trial, the ANZICS HEAT trial [32], has some superficial similarities to the Acetaminophen arm of the ASTER trial but did not target sepsis patients with organ dysfunction and used relatively low cumulative doses of Acetaminophen. In the HEAT trial, critically ill patients (n = 690) with fever were randomized to receive IV Acetaminophen or placebo 1g every 6h for up to 28 days, but only while febrile, leading to a median total dose of only 8g. This dose is significantly lower than our proposed total dose of 20g, which was chosen to provide continuous dosing over the early phase of sepsis during the time period when high levels of plasma CFH are present. Importantly, there was no signal for harm from Acetaminophen in the HEAT trial in terms of liver or other organ dysfunction or mortality. In summary, the HEAT trial does not provide any information about the efficacy of extended dosing of intravenous Acetaminophen in the target population that is of interest in ASTER and is relevant primarily with regards to safety of Acetaminophen in critical illness.

We will use the FDA-approved dose and frequency of intravenous Acetaminophen (1g every 6h or 4g/day, total dose 20 g; if weight < 50kg then dose reduced to 15 mg/kg every 6h). There are extensive safety data for Acetaminophen in healthy subjects receiving this dose and frequency enterally [33, 34]. Specifically, at this dose/frequency: (1) markers of liver injury are rarely elevated; (2) liver injury has not been observed until after 7 days of Acetaminophen use; and (3) any elevation of liver injury markers resolved after stopping the drug [33, 35]. Compared to enteral Acetaminophen, IV administration reduces initial hepatic exposure by approximately 2-fold through lack of first-pass metabolism [36, 37]. This dose of 1g IV every 6 hours was safe in 346 critically ill patients in the Acetaminophen arm in the HEAT trial with some patients receiving Acetaminophen at this dose for as long as 3 weeks [32]. In ASTER, the proposed duration of treatment is 5 days, rather than the 3 days studied in ACROSS. Treatment duration has been extended because our preliminary studies in critically ill patients enrolled in an ICU feeding trial [38], showed that high levels of plasma CFH persisted at 6 days (**Figure 5**). Acetaminophen should continue to be protective as long as the oxidative stimulus (CFH) is present; however, we elected to limit Acetaminophen treatment to 5 days to minimize any risk of hepatic injury.

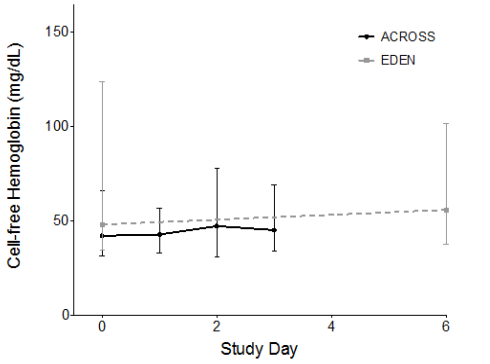


Figure 8. Comparison of plasma CFH levels in the ACROSS study (days 0,1,2,3) and the Vanderbilt phase 2 EDEN study (days 0, 6), a trial of different caloric intake goals in critically ill patients

3.4 Summary

Sepsis is common, associated with organ failure, high mortality, and currently without effective therapeutic interventions directed at the underlying pathophysiology. Acute lung injury (ARDS), acute kidney injury and cardiovascular dysfunction are common organ injuries in sepsis, are associated with increased mortality, and may be mediated, in part, by the elevated levels of CFH and pro-oxidant pathways that are characteristic of sepsis. Acetaminophen, a potent inhibitor of CFH-mediated oxidative injury, improves lung and renal function in pre-clinical models and seems to be potentially beneficial in humans with hemoprotein-mediated diseases, including in critically ill adults with sepsis.

ASTER was originally designed as an efficient platform for conducting two phase 2b trials with a shared placebo group in which we will assess the potential impact of Acetaminophen and Vitamin C on reducing organ injury in a population of patients with sepsis who have been prognostically enriched with evidence of either cardiovascular dysfunction or respiratory insufficiency (or both). The Vitamin C arm was stopped on June 15th and the trial will resume as a trial of Acetaminophen vs placebo. The trial will provide information on both the primary and secondary endpoints, including the biological endpoints, that will guide decisions in the future to proceed to larger phase 3 trials that would be focused on 90-day mortality. In addition, the results of this trial will establish whether a point-of-care measurement of the presence of cell-free hemoglobin should be used as a predictive enrichment strategy for selecting patients for future clinical trials of Acetaminophen. Also, it is important to note that intravenous Acetaminophen is readily available and inexpensive, increasing the potential impact of this trial.

4. Trial Design

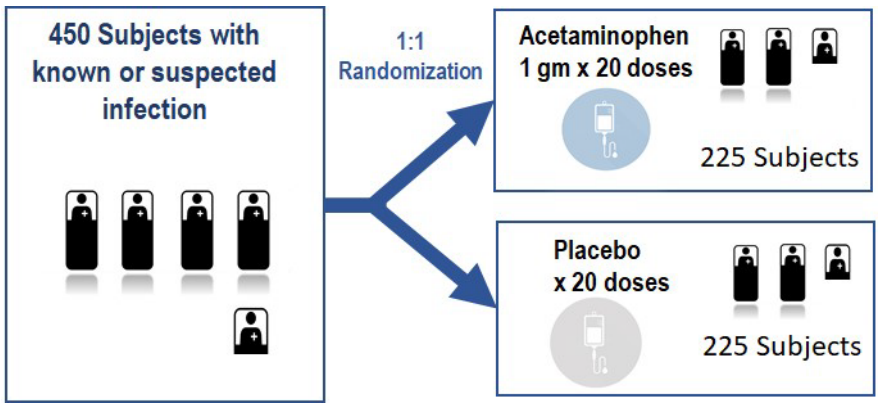
4.1 Study Description

Prospective multi-center phase 2b randomized placebo-controlled double-blinded interventional trial of intravenous Acetaminophen for patients with sepsis-induced hypotension or respiratory failure. Patients greater than or equal to 18 years old with known or suspected infection with associated hemodynamic or acute respiratory dysfunction will be eligible for enrollment.

Only subjects who are admitted or planned to be admitted to an intensive care unit (ICU) will be enrolled. Study drug administration will occur for a total of 120 hours, unless one of the following occurs:

1. Discharged from the study hospital;
2. Discharged from the ICU;
3. Withdrawal from study;
4. Death;
5. New AST or ALT elevation greater than 10 times the upper limit of normal level

A total of 450 participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 fashion (Acetaminophen:placebo) into the two treatment arms of the study. The two treatment arms are: Acetaminophen (225 patients) and Placebo (225 patients). Enrollment will occur over approximately 15 months.



The study interventions are:

1. Acetaminophen given intravenously at the dose of 1 gram (or 15 mg/kg if patient weighs < 50 kg) every six hours for 5 days (20 doses) ***OR***

2. Placebo (identical appearing 5% dextrose solution) infused every six hours for 5 days (20 doses)

The safety and efficacy will be evaluated through repeated laboratory assessment, clinical assessments and biomarker measurements during the entire study. Adverse events and clinical outcomes, including need for assisted ventilation, vasopressors, renal replacement therapy, ICU length of stay, and hospital length of stay, will be assessed through 28 days or hospital discharge, whichever occurs first. Hospital mortality and all-cause mortality at 90 days will also be assessed.

4.2 Randomization

After informed consent and completion of screening, we will randomize each eligible participant using a web-based randomization system. Designated research team members will have permission to randomize participants. At randomization, each subject will be assigned a unique randomization ID number that the site pharmacy can use to determine study arm assignment to Acetaminophen or placebo

The CCC will send a confirmation email to the randomizer containing the randomization ID number. We will stratify randomization by enrolling hospital.

4.3 Primary Efficacy Variable

Primary efficacy variables (days alive and free of assisted ventilation, vasopressors, and new renal replacement therapy) will be evaluated comparing Acetaminophen vs. placebo: over the first 28 days Patients need to be free of all three components to qualify for a day alive and free from organ failures. A patient could be free of all organ failures from day 10 through day 22 and then die on day 22 and would receive 12 days of credit for this primary outcome. The components of this outcome (days alive and free of assisted ventilation, vasopressors and new renal replacement therapy in the overall cohort and in survivors, and 28-day hospital mortality) will also be reported.

- This three-component primary outcome was chosen as preliminary data suggest the study intervention has the potential to reduce mortality and favorably impact at least two of the three organ failure support outcomes, thus increasing the sensitivity of this outcome for benefit in a Phase 2b trial designed primarily to assess safety and proof of concept [39, 40].

4.4 Secondary Clinical Efficacy Variables

The ventilator, vasopressor, new renal replacement, and hospital "free days" endpoints below are traditional Sepsis and ARDS Phase 2 and Phase 3 composite outcomes that assign a value of zero free days for participants dying on or before study day 28 to control for the competing risk of death as described in Section 8.3 of the protocol. These traditional outcomes are included in this Phase 2b trial to search for additional evidence of efficacy that could support a decision to progress to Phase 3 and will allow for comparison to other sepsis and ARDS trials using these endpoints, including all other PETAL studies.

1. 28-day ventilator-free days
2. 28-day vasopressor-free days
3. 28-day new renal replacement-free days
4. 28-day hospital mortality
5. 28-day ICU free-days
6. 28-day hospital-free days to discharge home
7. 28-day duration of ICU stay in survivors and non-survivors
8. Initiation of assisted ventilation to day 28
9. Initiation of renal replacement therapy to day 28
10. Change in organ-specific Sepsis-related Organ Failure Assessment (SOFA) scores between enrollment and study day 7 (Appendix B)
11. 90-day hospital mortality (includes death at any healthcare facility that is not the equivalent of home for a patient)
12. Development of ARDS within 7 days of randomization
13. Change in serum creatinine from enrollment to discharge, death, initiation of dialysis or 28 days, whichever occurs first
14. Major Adverse Kidney Events at 28 days (MAKE28): persistent increase in serum creatinine by 200% from baseline, need for new renal replacement therapy, or death
15. Change in the Radiographic Assessment of Lung Edema (RALE) score from enrollment to study day 3 in patients who are receiving assisted ventilation or high flow nasal oxygen at baseline.
16. 90-day all-cause mortality

NOTE: Please see section 8.3 for description of how these variables are defined and calculated.

4.5 Safety Variables

Safety monitoring and analysis will be performed separately on the Acetaminophen and placebo arms. The safety variables will include the following:

1. Allergic or allergic-like reactions such as urticarial drug rash, hyperemia with hypotension, and anaphylaxis
2. AST and ALT measured on study days 0, 2-5, and 7 (day 7 measurement can be ± 1 day)
3. The trough plasma levels measured just prior to a study dose of Acetaminophen on Day 2 (subject must have received at least 5 doses of study drug before the day 2 samples are obtained) in the first 100 patients will be reported to the DSMB to determine if they exceed the level of 20 micrograms/mL, the potential level for hepatotoxicity.
4. Administration of fluid bolus, new use of vasopressor, or increased dose of vasopressor within 120 minutes of study drug infusion.
5. Incidence of reported adverse events

4.6 Biological Endpoints

Change in plasma IL-6, angiopoietin-2, cell-free DNA, Syndecan-1, and cell-free hemoglobin between enrollment (baseline) and Days 2 and 3.

5. Treatments Arms and Study Drug Administration

All study drug will be administered by the bedside nurse to the patient through an indwelling peripheral or central venous access line. Study drug will be held if the patient loses all intravenous access and will be restarted as soon as intravenous access is restored. Missed doses will be recorded but will not be added on to the end of the study. If the patient is discharged from the ICU prior to day 5 or 20 doses, study drug will be stopped. A list of drug incompatibilities for Acetaminophen will be provided to each clinical site.

5.1 Acetaminophen Arm

Treatment: IV Acetaminophen
Dose: 1 gm (or 15 mg/kg if patient is less than 50 kg)
Frequency: Every 6 hours
Duration: 5 days (20 doses) or ICU discharge, whichever comes first

Patients randomized to Acetaminophen will receive Acetaminophen (hospital pharmacy stock) intravenously at the dose of 1 gram (or 15 mg/kg if patient < 50kg) every 6 hours for a maximum of 5 days (20 doses). Intravenous Acetaminophen was chosen over enteral Acetaminophen to insure adequate drug delivery in critically ill patients. In the ACROSS trial of enteral Acetaminophen (1 g every 6 hours), the observed serum Acetaminophen levels were at the lower limit of the therapeutic window (**Figure 9**). Intravenous Acetaminophen is expected to provide higher peak levels of Acetaminophen while avoiding first pass metabolism by the liver. Based on the observation that cell-free hemoglobin levels remain elevated at 6 days in critically ill patients (see **Figure 5, section 3.3**), treatment will be continued for 5 days (for a maximum of 20 doses) or until any of the following occur:

1. Discharged from the study hospital;
2. Discharged from the ICU;
3. Withdrawal from study;
4. Death;
5. New AST or ALT elevation greater than 10 times the upper limit of normal level.

For blinding purposes, Acetaminophen will be transferred to a sterile INTRAVIA container (Baxter) or its equivalent prior to dispensing by the pharmacy.

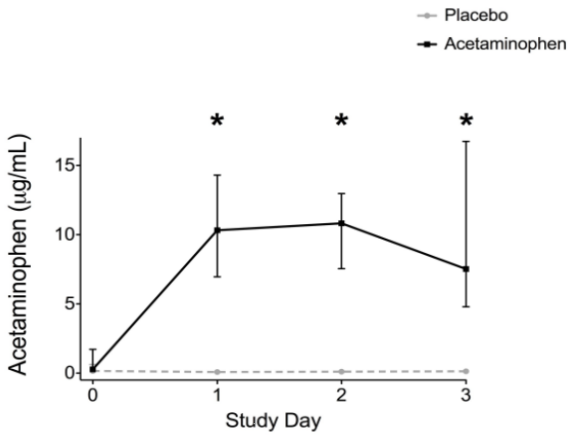


Figure 9. Serum Acetaminophen levels on enrollment and each study day of the ACROSS trial of enteral Acetaminophen versus placebo in sepsis

5.2 Placebo Arm

Treatment: Placebo
Dose: 5% dextrose in water
Frequency: Every 6 hours
Duration: 5 days (20 doses) or ICU discharge, whichever comes first

Patients randomized to Placebo arm will receive an identical appearing room temperature 5% dextrose in water placebo intravenously every 6 hours for a maximum of 5 days (for a maximum of 20 doses). A similar placebo has been used in other randomized clinical trials of IV Acetaminophen. The =-Placebo will be 100 ml of 5% dextrose in water. Patients weighing <50 kg will receive a similar weight-adjusted volume to patients in the active treatment arm. Treatment will stop at 5 days (20 doses) or until any of the following occur:

1. Discharged from the study hospital;
2. Discharged from the ICU;
3. Withdrawal from study;

4. Death;
5. New AST or ALT elevation greater than 10 times the upper limit of normal level.

5.3 Drug Interruptions

Interruptions of study drug should be avoided. If the study drug must be interrupted due to loss of intravenous access, it should be restarted as soon as the treatment team re-establishes intravenous access. In cases in which the study drug was interrupted, the missed doses will not be added on to the end of the study. If a dose cannot be administered within 3 hours of the scheduled time, the dose should be skipped. Any dose administered outside of the +/- 1-hour window or any dose that is skipped will trigger a protocol deviation.

Any study drug interruptions will be recorded, including the reason for the interruption.

In the case of a new measurement of an AST or ALT greater than or equal to 10 times the upper limit of normal or rash or other hypersensitivity attributed to the study drug during the study period, the study drug will be stopped and not restarted. Elevation of AST or ALT is known to reverse with discontinuation of Acetaminophen [32]; in almost all cases simply discontinuing the study drug is appropriate. If study drug is discontinued for AST and/or ALT elevation we will repeat AST and ALT at 24 and 48 hours after the study drug is discontinued and continue to measure daily until the levels have declined from their peak level.

6. Study Population and Enrollment

6.1 Participant Enrollment

The study is expected to accrue over approximately 15 months. Participants will be recruited from the Emergency Department or Intensive Care Unit at PETAL Network centers. Participants who withdraw or prematurely discontinue study drug will be analyzed by an intention to treat analysis. Safety data will continue to be collected up to hospital discharge for any participants who are withdrawn from the study.

6.2 Inclusion Criteria

1. Age ≥ 18 years
2. Sepsis defined as:
    a. Clinical evidence of a known or suspected infection and orders written to administer antibiotics

    AND

    b. Hypotension as defined by the need for any vasopressor (and 1 liter of fluid already administered intravenously for resuscitation) **OR** respiratory failure defined by mechanical ventilation, BIPAP or CPAP at any level, or greater than or equal to 6 liters/minute of supplemental oxygen (criterion b must be present at the time of randomization)
3. Admitted (or intent to admit) to a study site ICU within 36 hours of presentation to the study site ED or within 36 hours of presentation to any acute care hospital

6.3 Exclusion Criteria

1. No consent/inability to obtain consent from the participant or a legally authorized representative
2. Patient unable to be randomized within 36 hours of presentation to the ED or within 36 hours of presentation to any acute care hospital
3. Diagnosis of cirrhosis by medical chart review
4. Liver transplant recipient
5. AST or ALT greater than five times the upper limit of normal
6. Diagnosis of ongoing chronic alcohol use disorder/abuse by chart review; if medical record unclear, use Appendix F
7. Hypersensitivity to Acetaminophen
8. Patient, surrogate or physician not committed to full support (Exception: a patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest)
9. Home assisted ventilation (via tracheotomy or noninvasive) except for CPAP/BIPAP used only for sleep-disordered breathing
10. Chronic dialysis
11. Use of home oxygen > *3 liters/min nasal cannula* for chronic cardiopulmonary disease
12. Moribund patient not expected to survive 24 hours
13. Underlying malignancy or other condition with estimated life expectancy of less than 1 month
14. Pregnant woman, woman of childbearing potential without a documented negative urine or serum pregnancy test during the current hospitalization, or woman who is breast feeding
15. Prisoner
16. Treating team unwilling to enroll because of intended use of Acetaminophen

6.4 Reasons for each of the exclusion criteria

1. No consent/inability to obtain consent – *no justification for waiver of informed consent.*
2. Patient unable to be randomized within 36 hours of presentation: limits enrollment to acute conditions and presentations.
3. Diagnosis of cirrhosis – *not safe to administer 4 grams of IV Acetaminophen daily in this clinical setting*
4. *Liver transplant recipients are excluded as the doses of acetaminophen used in this study exceed recommended doses for liver transplant patients*
5. AST or ALT greater than five times the upper limit of normal – *this is a standard precaution to exclude patients with acute or chronic liver disease [38].*
6. Diagnosis of ongoing chronic alcohol use disorder/abuse – *these patients may have an increased risk of hepatic toxicity from Acetaminophen.*
7. Hypersensitivity to Acetaminophen– *self-evident.*

8. ICU staff, legally authorized next of kin or study subject not committed for full support – *required to assess the potential beneficial effects of Acetaminophen on the primary and secondary outcomes.*
9. Home assisted ventilation (via tracheotomy or noninvasive) except for CPAP/BIPAP used only for sleep-disordered breathing – *these patients would have ventilator dependent respiratory failure.*
10. Chronic dialysis is excluded because one component of the primary end-point is days free of dialysis over the first 28 days in the trial.
11. Use of home oxygen > *3 liters/min nasal cannula* for chronic cardiopulmonary disease- *these patients with severe chronic respiratory failure may not be a good candidate for an intervention designed in part to facilitate lung injury resolution.*
12. Moribund patient not expected to survive 24 hours – *these patients would not fit the goals of testing an intervention designed to reduce organ failure from sepsis.*
13. Underlying malignancy or other condition with estimated life expectancy of less than 1 month - *these patients would not match with the secondary outcome of testing the beneficial effects of this therapy on 28-day mortality.*
14. Pregnant female, female of childbearing potential without a documented negative urine or serum pregnancy test during the current hospitalization, or female who is breast feeding – *safety not established for using the intervention to be tested in this trial.*
15. Prisoner – *not correct to include these patients in clinical trials by ethical standards.*
16. Treating team unwilling to enroll because of intended use of Acetaminophen– *open label Acetaminophen use is prohibited in this trial because the study drug dose is the maximum FDA approved dose and would also confound interpretation of the results of the trial.*

6.5 Co-enrollment

Co-enrollment in other clinical trials will only be allowed after a trial has been approved for co-enrollment by ASTER study leadership and the PETAL DSMB. Interventions that are contraindicated in combination with acetaminophen are not permitted. Study procedures of the co-enrolling trial must not impose an undue burden on research participants or research staff when viewed within the context of ASTER study procedures, including the total volume of blood drawn for research and follow-up activities. For blinded trials, the co-enrolling trial must agree to confidentially provide unblinded treatment assignments to the respective DSMBs and the unblinded Medical Monitors to allow for accurate assessment of serious adverse events and unanticipated problems.

6.6 Informed Consent

Screening will occur in the Emergency Department and intensive care units daily to identify potential candidates for enrollment. Once a potential participant is identified, the patient's primary medical team will be contacted to secure permission to approach the patient or their legally authorized representative regarding possible participation in the study. If the primary team agrees, the study coordinator or investigator will meet with the patient and/or legally authorized representative and will describe the proposed study protocol in lay terminology. Prior to performing any study procedures, an informed consent form (ICF) approved by the central IRB will be signed and dated by each study participant or legally authorized representative and the study investigator or person informing the subject and obtaining the

consent. Prior to taking part in the study, the participant or his or her legal representative will receive a copy of the signed and dated ICF.

A special vulnerable population, cognitively impaired patients, will be eligible for enrollment in this proposed study. Many septic patients have cognitive impairment as part of their acute disease process and others require sedation during their treatment course. In cases where the potential participant is cognitively impaired, surrogate consent will be obtained from the participant's legally authorized representative according to local state law. In these cases if the cognitive impairment has resolved prior to hospital discharge, the participant will be reconsented at the earliest opportunity and given the option of continuing or stopping their participation.

6.7 Excluded Medications

Clinicians will be prohibited from administration of Acetaminophen (either intravenously or enterally) to study participants during the study. Additionally, administration of open label Acetaminophen at any dose will be recorded in the case report forms.

6.8 On-study Fever Management Recommendations

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) or Cyclooxygenase-2 inhibitors to treat fever and pain will be discouraged during the 5-day study drug administration and the use of these medications for other indications will also be discouraged. No restriction will be placed on the use of aspirin in doses of less than or equal to 325 mg per day.

The use of open-label acetaminophen will not be permitted while receiving study medication. Once the course of study drug administration has been completed, open-label acetaminophen can be administered at the discretion of the treating clinician. Physical cooling will be used at the discretion of the clinical team per local practice preferences.

This plan will apply to both the Acetaminophen and placebo arms Fever Management Recommendations are also outlined in the Appendix.

6.9 Concomitant Medications

We will record use of non-steroidal anti-inflammatory agents, iodinated contrast, glucocorticoids (all preparations including hydrocortisone, methylprednisolone, prednisone, dexamethasone), thiamine, remdesivir, baricitinib, tocilizumab.

6.10 Common Strategies for Study Participants

6.10.1 Ventilator Procedures

Low tidal volume ventilation and weaning from mechanical ventilation will follow standard clinical protocol for participants meeting criteria for ARDS (Appendix C).

Low Tidal Volume Ventilation: We will use a simplified version of the ARDS network 6 ml/kg PBW lung protective ventilation protocol. If not already being used, a low tidal volume protocol for mechanical ventilation must be initiated within two hours of randomization in all patients who meet criteria for ARDS.

Weaning: Since the time at which 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 also be controlled by protocol rules in accordance with these evidence-based recommendations. This weaning strategy is a simplified version of the protocolized weaning strategy used in prior PETAL and ARDS Network studies.

6.10.2 On Study Fluid Management

Fluid management during shock will be unrestricted. Balanced crystalloid solution (such as lactated Ringers, Hartman's solution, Plasmalyte or Normosol) is preferred, for resuscitation. Given the lack of clear evidence identifying a superior approach, the type of fluid administered will not be mandated.

However, in patients not in shock or after shock resolution, a conservative fluid approach will be recommended for patients with ARDS. This conservative fluid management approach is a simplification of the algorithm utilized in the ARDS Network FACTT study (Appendix D).

6.12 Criteria for Discontinuation or Withdrawal

The primary reason for treatment discontinuation will be recorded using the following categories:

a. Adverse Event: The participant has experienced an adverse event that the investigator believes requires early termination because continued participation imposes an unnecessary risk to the participant's health.

b. Major Protocol Deviation: The participant failed to meet protocol entry criteria or did not adhere to protocol requirements, excluding prolonged interruption of study drug.

c. Voluntary Withdrawal: The participant or legally authorized representative wishes to withdraw from the study. The reason for withdrawal, if provided, will also be documented in the CRF.

d. Other: This category includes participants withdrawn by the treating team for a new indication for Acetaminophen use.

7.0 Study Plan

7.1 Baseline Assessments

The following 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.

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, ICU
5. Vital signs: heart rate (beats / min), systemic systolic and diastolic BP (mmHg), body temperature (°C), and oxygen saturation with FiO_2
6. Use of vasopressors, corticosteroids, acetaminophen, thiamine, supplemental O2, oxygen saturation, invasive or non-invasive/invasive mechanical ventilation and renal replacement therapy prior to randomization
7. Clinical laboratory testing results (AST, ALT, total bilirubin, serum bicarbonate)
8. Serum creatinine:
    a Prehospitalization: Most recent outpatient creatinine from 24 hours to 365 days prior to admission if available
    b Baseline: Lowest in hospital creatinine prior to randomization
9. Chest radiograph
10. ARDS assessment if receiving assisted ventilation
11. Presumed site of primary infection
12. SOFA Score: as described in Appendix B
13. Glasgow Coma Score
14. Cell free plasma hemoglobin (to be collected and measured in batch at the end of the study)
15. COVID-19 status and date of first positive test if known within 3 weeks of enrollment

7.2. Assessments During Protocol Phase (through study day 7)

1. Daily fluid administration for the first 7 days (truncated for death or ICU discharge)
2. Daily fluid outputs for the first 7 days (truncated for death or ICU discharge)
3. Chest radiograph on day 3 (± 1 day) for all patients who were receiving assisted ventilation or high flow nasal oxygen at the time of randomization if they are still in the study hospital
4. ARDS assessment through study day 7 (± 1 day). We will determine the presence and severity of ARDS for each day of assisted ventilation to day 7 using the following approach. For participants on assisted ventilation with P/F <300 or S/F <315, 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 S/F <315 (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.

6. AST and ALT, and bilirubin on days 1-7 if available. **AST/ALT REQUIRED on days 2-5, and 7 (day 7 measurement can be ±1 day).** Daily SOFA score through day 7 or hospital discharge
7. Recording of fluid bolus (500 mL or more), new vasopressor administration, or increase of vasopressor dose within 120 minutes of receiving study drug
8. Administration of the following concomitant medications: non-steroidal anti-inflammatory agents, iodinated contrast, glucocorticoids, thiamine, remdesivir, baricitinib, and tocilizumab

7.3. Other Assessments and Data Collection

1. Vasopressor use over 28 days
2. Study drug administration
3. Use of invasive and non-invasive ventilation (except noninvasive ventilation solely for sleep disordered breathing) over 28 days
4. New renal replacement therapy over 28 days
5. Last creatinine prior to initiation of RRT, death, study hospital discharge, or day 28 (whichever comes first)
6. Highest creatinine between randomization and day 28.
7. Results of microbiologic testing from samples taken from up to 24 hours prior to randomization until 72 hours after randomization
8. Source of infection

7.4. Assessments after Hospitalization

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.

7.5. 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. We will use publicly available data sources and the national death index as a final check for patients with whom we are unable to confirm their vital status through other means.

7.6. Specimen Collection

Plasma: Blood will be collected within 2 hours of randomization (prior to first study drug administration) and on days 2 and 3 (approximately 36 mls total). To minimize hemolysis, blood will preferentially be collected through central venous access devices if present. If there is no central venous access, then either an arterial or peripheral venous stick can be used, with blood drawn slowly to minimize hemolysis. The blood samples will be centrifuged, and the plasma will be frozen and stored at a biorepository for future research for the following purposes:

- ***Biological Endpoint Assays:*** To fulfill the secondary biological endpoints, the plasma samples will be measured for the concentration of plasma IL-6, angiopoietin-2, Syndecan-1, and cell-free DNA on enrollment and on days 2 and 3 and analyzed for significant changes from baseline in the placebo and Acetaminophen groups.
- ***Additional Assays:*** In addition, the plasma samples at baseline and on days 2 and 3 will be used to measure cell-free hemoglobin.
- ***Acetaminophen Levels:*** Plasma collected as a trough level just prior to a study dose on Day 2 (subject must have received at least 5 doses of study drug before the day 2 samples are obtained) will be used to measure Acetaminophen levels in the first 100 patients randomized to the Acetaminophen arm. Measuring Acetaminophen levels in critically ill patients with sepsis will address a knowledge gap in the literature and contribute to interpretation of the results of the trial and also provide data that the DSMB can review after 100 patients are enrolled in the Acetaminophen arm. For the first 100 patients in the acetaminophen arm, the blood drawn on day 2 (between 8 am and 2 pm) will be timed to occur 30 minutes before the next study drug administration (for a trough level of acetaminophen).
- ***Samples for Future Research:*** Plasma that has not been used for these planned assays will be stored in a biorepository for future research funded by ancillary studies.

Whole Blood for Genetics: When consent for genetic testing is specifically obtained, additional whole blood for future RNA and DNA studies will be collected at baseline and on day 3. Total blood volume for the genetic samples is approximately 8.5 ml/day, or 17mls total. Total overall blood volume collected (plasma and DNA/RNA) is approximately 53 ml.

Urine: Urine will be collected within 2 hours of randomization and on days 2 and 3 (if patient still in the ICU), frozen and stored along with plasma. Urine samples will be saved for ancillary studies.

Storage and Shipment: All samples collected in this trial will be identified by a coded number during shipment and storage at the central biorepository.

8. Statistical Methods

8.1 Primary Endpoint

The primary endpoint of this trial is to evaluate the effects of intravenous Acetaminophen compared to placebo on the number of days alive and free of assisted ventilation, vasopressors and new renal replacement therapy between the treatment arm and the placebo group over the first 28 days.

Note that the primary outcome components to be reported will be:

1. 28-day mortality prior to discharge home
2. Days free of assisted ventilation to day 28 in the overall cohort and survivors
3. Days free of new RRT to day 28 in the overall cohort and survivors
4. Days free of vasopressors to day 28 in in the overall cohort and survivors

The primary safety objective is to determine the effect of intravenous Acetaminophen on markers of liver injury (AST and ALT) measured on days 2-5, and 7 (day 7 measurement can be ±1 day).

8.2 Sample Size

The primary study outcome is 28-day organ support free days (alive and without assisted ventilation, new renal replacement and vasopressors). Using clinical trial data from the PETAL Network, the estimated standard deviation of 28-day organ support free days (obtained from the PETAL Network CLOVERS study) is 8.7 days. With a sample size of 225 in the active treatment group, and 225 in the r placebo treatment group, a two sample Z-test will have 85% power at a two-sided alpha level of 0.05 to detect a significant difference between active treatment and placebo if the true mean difference is 2.5 support free days. .We will target a total enrolment of 450 participants to offset a 2% rate of loss to follow up.

8.3 Secondary endpoints

We will compare the efficacy of intravenous Acetaminophen to placebo for efficacy endpoints. We will compare the safety of Acetaminophen to placebo for safety endpoints.

- **28-day ventilator-free days:** 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 days of invasive or noninvasive ventilation to day 28. 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. 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.
- **28-day vasopressor-free days:** Vasopressor 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 the use of vasopressor therapy. Patients who die prior to day 28 and those who receive vasopressor therapy for the entire first 28 days are assigned zero vasopressor free days.
- **28-day new renal replacement-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 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.
- **28-day hospital mortality**
- **28-day ICU free days:** ICU free days to day 28 are defined as the number of days spent alive and out of the ICU to day 28.
- **28-day hospital free days to discharge home:** 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.

- **Duration of ICU stay in survivors and non-survivors**: The total number of days spent in the ICU until hospital discharge or death during the first 28 days. If a patient is discharged alive from the study hospital we assume they are no longer in the ICU.
- **Initiation of assisted ventilation to day 28**: Any patient who received assisted ventilation in the first 28 days meets this endpoint. If a patient leaves the hospital without initiation of assisted ventilation, we assume they never started.
- Initiation of new renal replacement therapy to day 28.
    - Patients who receive (new) renal replacement therapy through day 28 will meet this endpoint.
- **Change in organ-specific Sepsis-related Organ Failure Assessment (SOFA) scores between enrollment and day 7:** We will calculate the SOFA score upon enrollment and at day 7 using clinically available data. If a value is not available at baseline, it will be assumed to be normal. At the day 7 assessment, if a value is missing then we will carry forward the closest previously known value. The GCS component of the SOFA score will be omitted. (See Appendix B)
- 90-day hospital mortality (any hospital)
- **Development of ARDS within 7 days:** We will determine the presence and severity of ARDS for each day of assisted ventilation to day 7. For participants on assisted ventilation 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 are 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.
- Change in serum creatinine from enrollment to discharge, death, initiation of dialysis, or day 28, whichever occurs first.
- Major Adverse Kidney Events at 28 days (MAKE28): persistent increase in serum creatinine by 200% from baseline (defined as most recent outpatient creatinine from 24 hours to 365 days prior to admission if available: if not available, lowest in hospital creatinine prior to randomization), need for renal replacement therapy, or death
- Change in Radiographic Assessment of Lung Edema (RALE) score from enrollment to study day 3 in patients who are receiving assisted ventilation or high flow nasal oxygen at the time of study randomization
- The safety of intravenous Acetaminophen compared to placebo as measured by daily serum AST, ALT, blood pressure following study drug administration (both arms) and incidence of reported adverse events (both arms)

- Change in plasma IL-6, plasma IL-8, plasma angiopoietin-2, plasma cell-free hemoglobin, syndecan-1, and plasma cell-free DNA from enrollment to days 2 and 3
- **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 patients with whom we are unable to confirm their vital status through other means.

8.4 Safety Endpoints

AST and ALT will be measured on days 2, 3, 4, 5, and 7 after study enrollment. We will also collect data daily on potential adverse reactions to Acetaminophen, such as rash and hypersensitivity. If either are present and thought to be due to the study drug, the study drug will be stopped.

8.5 Predictive Biomarker Analysis

We will evaluate the predictive value of baseline plasma CFH for identifying patients who have an improvement in the primary endpoint, the three components of the primary endpoint, 28-day mortality or improvement in renal function as assessed by MAKE28.

8.6 Statistical Analysis Plan

The principal analyses will be intention-to-treat (based upon randomization assignment). A comprehensive statistical analysis plan will be written prior to the un-blinding of the primary and secondary efficacy results.

8.6.1 Sub-Group by Treatment Interaction

We will do a sub-group by treatment interaction analysis comparing outcomes in acute COVID-19, defined as a positive diagnostic test for SARS CoV-2 in the prior three weeks and pneumonia as primary site of infection, and COVID-19 negative patients for the primary and secondary efficacy endpoints. The analysis will include a tabulation of the treatment effect in COVID-19 positive patients, the treatment effect in COVID-19 negative patients, and the difference between the treatment effect in these two sub-groups. We will also apply this interaction analysis separately to two additional pre-randomization factors, received acetaminophen (yes versus no), and home oxygen requirement (yes versus no).

8.7 Interim Analysis

The DSMB will have the ability to analyze all safety data, including AST/ALT, at any time during the study and stop the study indefinitely for safety reasons. The safety report will include a tabulation of all baseline demographics and physiologic variables as well as on-study variables, including SOFA scores, and all adverse events by randomized groups. For monitoring safety, data on 28-day mortality will be included with 95% confidence intervals for any differences between placebo and the acetaminophen group. In addition, a formal safety analysis will be done after 225 patients are accrued. This report will include an analysis of acetaminophen levels. Trough levels greater than 20 mcg/mL will be evaluated for any relationship to AST/ALT levels. Investigators will recommend protocol modification as needed to the DSMB as part of the safety review.

Based on an interim analysis of the primary efficacy variable, this trial may stop for efficacy or futility of APAP relative to placebo. The stopping rules are based on two stage Haybittle-Peto stopping boundaries [42, 3] with Z=3.4 for early efficacy stopping. We plan one interim look at approximately one half of total enrollment and a final look at full enrollment.

Table 1 below presents the stopping boundaries as a function of the mean difference in the primary efficacy variable favoring active treatment and the one-sided p-value favoring active treatment. **Tables 2** and **3** present the probability of stopping at stage one under the null and alternative hypotheses respectively. As can be seen in Table 2 the probability of stopping early for futility under the null is 10%. Table 3 shows that the probability of stopping early for efficacy under the alternative is also 10%.

Table 1. Stopping Boundaries

n	Futility Bound Mean Difference	Efficacy Bound Mean Difference	Futility Bound P-value	Efficacy Bound P-value
~218	-1.51088	4.01088	0.89986	0.0003369
436	1.63584	1.63584	0.02493	0.02493

Table 2. Stopping probabilities given the null hypothesis

Stage	Futility	Efficacy
1	0.10014	0.00034

Table 3. Stopping probabilities given the alternative hypothesis

Stage	Futility	Efficacy
1	0.00034	0.10014

9.0 Risk Assessment

This study involves randomization to one of two groups: Acetaminophen or placebo within 36 hours of meeting inclusion. Patients will all be closely monitored in an ED or ICU setting. This will allow for prompt treatment of any suspected adverse events, including liver injury. Adverse events resulting in discontinuation of study drug will be reported to the DSMB as noted in section 11.1 and Appendix E.

9.1 Potential Risks to Subjects

Risk of Acetaminophen Administration: Serum AST and ALT will be monitored as part of the study on study days 0 and days 2-5. New measured values of AST or ALT greater than or equal to 10 times the upper limit of normal on any measurement will prompt discontinuation of the study drug, which will not be restarted. Elevations in AST and ALT are common as a result of severe sepsis regardless of an interventional trial, are rarely associated with this dose and schedule of Acetaminophen, and do not require any changes in therapy other than stopping of the study drug. Therefore, the risk of AST or ALT elevation will be included in the informed consent. AST or ALT elevations greater than 10 times the upper limit of normal will be considered serious adverse events. Reporting of all adverse events to the DSMB will be done

in a blinded fashion. In addition to reporting these events to the DSMB, all events will also be included in the annual review by the IRB.

Hypotension is uncommon but a described occurrence with intravenous Acetaminophen administration (frequency of 1% per manufacturer's package insert) that appears to occur predominantly in patients with fever. We will monitor the need for a fluid bolus (500 ml or more), the need for a new vasopressor, or an increase in the vasopressor dose in the 120 minutes following administration of the study drug. Risk of hypotension will be included in the informed consent.

Risk of Placebo Administration: Minimal risk because the volume of administration of 5% Dextrose in water is only 100 ml every 6 hours for 120 hours.

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 is 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.

9.2 Risk of Death

It is possible that the treatment arm may lead to more deaths in comparison to placebo; mortality will be reported to the DSMB at the interim and final analyses.

9.3 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.

9.4 Potential Benefits

Study subjects may or may not receive any direct benefits from their participation in this study. It is unclear whether Acetaminophen will provide benefit. Thus, the optimal treatment with Acetaminophen is undefined at this point.

9.5 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.

10. 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.

10.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The EDs and the ICUs 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.

10.2 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 or acute respiratory failure. Due to the nature of sepsis induced hypotension and respiratory failure, most 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.

10.3 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.

10.3.1 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

ASTER 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 (method 3).

Method 1 Paper-based approach:

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.

Method 2 Paper-based approach:

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.

Method 3 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.

10.4 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.

10.5 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.

10.6 Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol will 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.

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 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 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 [44]. 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 [44].

10.7 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 [45]. 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." [46]. 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…" [44]. 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.

10.8 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.

10.9 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.

11. Adverse Events

11.1 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 10** (five days after completion of the study drug infusions) or hospital discharge, whichever occurs first and will determine if such adverse events are reportable.

The following adverse events will be considered reportable and thus 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 E)
- Study-specific clinical outcomes (Primary and Secondary Outcomes and Assessments During the Study), including serious adverse events such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug or the conduct of study procedures (or of uncertain relationship) as outlined in Appendix E.

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 the study drug or 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 E. Investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the protocol and the investigator brochure for intravenous Acetaminophen. Investigators will also determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

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.

11.2 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 E 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:

- Death
- 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.

Reportable serious adverse 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 **10 study days** or until hospital discharge, whichever occurs first, regardless of the investigator's opinion of causation.

Appendices

A. Schedule of Events

Measurement/Event		Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 28	Day 90
Demographics, history and physical		X									
Collect with Study Samples:	Cell-free hemoglobin (not point of care)	X		X	X						
	Angiopoietin-2, syndecan-1, & IL-6	X		X	X						
	Cell Free DNA	X		X	X						
	APAP trough level			X							
HCG (if female of childbearing age)		X									
Charlson score		X									
Serum Bicarbonate		A									
COVID-19 status and date of test (capture if dx is within 3 weeks of admission)		A									
Non-study administration of acetaminophen		X	X	X	X	X	X				
Vital signs		X	X	X	X	X	X	X	X		
Vasopressor use		X	X	X	X	X	X	X	X		
O2, non-invasive and invasive ventilation		X	X	X	X	X	X	X	X		
Daily fluid balance (intake and output)			X	X	X	X	X	X	X		
Serum creatinine (see below for pre/baseline/on study breakout)*		A	A	A	A	A	A	A	A	A	
Chest radiograph		A	A	A	A	A	A	A	A		
ARDS assessment		X	X	X	X	X	X	X	X		
Study drug administration***		X	X	X	X	X	X				
Liver function tests [AST, ALT]**		X	A	X	X	X	X	A	X		
Administration of Concomitant Medications	Thiamine		X	X	X	X	X	X	X		
	Iodinated contrast administration		X	X	X	X	X	X	X		
	Glucocorticoids		X	X	X	X	X	X	X		
	Non-steroidal anti-inflammatory agents		X	X	X	X	X	X	X		
	Remdesivir, baricitinib, & tocilizumab		X	X	X	X	X	X	X		
Blood collection for study samples	Plasma	X		X[a]	X						
	DNA	X			X						
	RNA	X			X						
Urine collection (only if in the ICU)		X		X	X						
SOFA score		X	X	X	X	X	X	X	X		
Microbiology results (i.e., positive blood culture results)		A	A	A	A						
Outcome Data	Disposition (ICU and hospital status)									X	
	Ventilator, vasopressor, & renal replacement therapy use									X	
	Assessment of infection source									X	
	Vital status									X	X

X = Required; **A** = When clinically available

* ***Creatinine:***

- ***Prehospital:*** *Most recent outpatient creatinine from 24 hours to 365 days prior to admission if available*
- ***Baseline:*** *Lowest in hospital creatinine prior to randomization*
- ***On study:*** *Collect peak creatinine between randomization and study day 28 and last creatinine value prior to death, RRT, discharge from study hospital, or day 28 (whichever comes first)*

** ***Liver Function Tests;:*** *These values are required on days 2-5, and 7 (day 7 can be collected ± 1 day).*

[a] ***Day-2 Plasma:*** *Collect **30 minutes prior to study drug administration**; subject must have received at least 5 doses of study drug before the day 2 samples are obtained). One aliquot of Day 2 collection will be designated for **Acetaminophen trough level**.*

*** *First dose of study drug should be administered within 4 hours of randomization (Day 0). In the 120 minute interval following all study drug doses, instances of the administration of fluid boluses, new vasopressors, and increases in vasopressor doses will be recorded including maximum fluid volume, vasopressor dose, or greatest increase in vasopressor dose.*

B. Sequential (Sepsis-related) Organ Failure Assessment (SOFA) Score

SOFA Score	0	1	2	3	4
Pulmonary (PaO_2/FiO_2, mmHg)	≥ 400	< 400	< 300	< 200	< 100
Coagulation (Platelets x $10_3/mm_3$)	≥ 150	< 150	< 100	< 50	< 20
Liver (Total Bilirubin, mg/dL)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12.0
Cardiovascular (Mean Arterial Pressure, mmHg)	≥ 70	< 70	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1*	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1*
Renal (Serum Creatinine, mg/dL)	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	≥ 5.0

*Adrenergic agents administered for at least 1 hour, doses given as µg/kg/min

C. Ventilator Management for Patients with ARDS

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW) in kilograms

   Males = 50 + 2.3 [height (inches) - 60]

   Females = 45.5 + 2.3 [height (inches) -60]

2. Controlled ventilation mode required during NMB. After NMB, select any ventilator mode capable of delivering the prescribed V_T (6ml/kg PBW, +/- 2 ml/kg)

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%

1. Use a minimum PEEP of 5 cm H_2O.
2. Adjust FiO_2 or PEEP upward within 5 minutes of consistent measurements below the oxygenation target range
3. Adjust FiO_2 or PEEP downward within 30 minutes of consistent measurements above the oxygenation target range.
4. The below PEEP strategy FiO2/PEEP table should be used in all patients.

PEEP/FiO2

FiO_2	.30	.40	.40	.50	.60	.70	.80	.90	1.0
PEEP	5	5	8	8-10	10	10-14	14	14-18	18-24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O

Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T.

- **If Pplat > 30 cm H_2O**: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).
- **If Pplat < 25 cm H_2O and V_T< 6 ml/kg**, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or V_T = 6 ml/kg.
- **If "severe dyspnea"** (more than 3 double breaths per minute or airway pressure remains at or below PEEP level during inspiration), then raise V_T to 7 or 8 ml/kg PBW if Pplat remains below 30. If Pplat exceeds 30 cm H_20, then revert to lower V_T and consider more sedation.

pH GOAL: ≥ 7.30

- If pH < 7.30: May give $NaHCO_3$ (neither encouraged nor discouraged)
- If pH < 7.15: V_T may be raised and Pplat limit suspended (neither encouraged nor discouraged)
- If pH < 7.30: incremental increase in RR allowed to max rate of 35.

I:E RATIO GOAL: Recommend that duration of inspiration be ≤ duration of expiration.

PART II: WEANING

Conduct a SPONTANEOUS BREATHING TRIAL daily when:

- FiO_2 ≤ 0.40 and PEEP ≤ 8
- PEEP and FiO_2 ≤ values of previous day
- Systolic BP ≥ 90 mmHg and without vasopressor support
- Spontaneous respirations

SPONTANEOUS BREATHING TRIAL (SBT):

If all above criteria are met initiate a trial of UP TO 120 minutes of spontaneous breathing with FiO2 ≤ 0.5 using any of the following approaches:

- Pressure support ≤ 5cm H_2O, PEEP ≤ 5cm H_2O
- CPAP ≤ 5 cm H_2O
- T-piece
- Tracheostomy mask

Definition of UNASSISTED BREATHING

1. Extubated with face mask, nasal prong oxygen, or room air, **OR**
2. T-tube breathing, **OR**
3. Tracheostomy mask breathing, **OR**
4. CPAP less than or equal to 5 cm H_20 **without pressure support or IMV assistance OR**
5. Use of CPAP or BIPAP solely for sleep apnea management

Assess for tolerance using the following:

- SpO_2 ≥ 90: and/or PaO_2 ≥ 60 mmHg
- Spontaneous V_T ≥ 4 ml/kg PBW
- RR ≤ 35/min
- pH ≥ 7.3
- No respiratory distress (distress = 2 or more of the following):
  - HR > 120% of baseline
  - Marked accessory muscle use
  - Abdominal paradox
  - Diaphoresis
  - Marked dyspnea

If tolerated for at least 30 minutes, consider extubation.

If not tolerated resume pre-weaning settings.

D. On-Study Fluid Management for Patients with ARDS

This protocol should be initiated after the initial resuscitation.

- Discontinue maintenance fluids.
- Continue medications and nutrition.
- Manage electrolytes and blood products per usual practice.
- For shock, use any combination of fluid boluses[#] and vasopressor(s) to achieve MAP ≥ 60 mmHg as fast as possible. Wean vasopressors as quickly as tolerated beginning four hours after blood pressure has stabilized.
- Withhold diuretic therapy in renal failure [§] and until 12 hours after last fluid bolus or vasopressor given.

CVP (recommend)	PAOP (optional)	MAP ≥ 60 mm Hg AND off vasopressors for ≥ 12 hours	
		Average urine output < 0.5 ml/kg/hr	Average urine output ≥ 0.5 ml/kg/hr
>8	> 12	Furosemide* Reassess in 1 hour	Furosemide* Reassess in 4 hours
4-8	8-12	Give fluid bolus as fast as possible[#] Reassess in 1 hour	
< 4	< 8		No intervention Reassess in 4 hours

§ Renal failure is defined as dialysis dependence, oliguria with serum creatinine > 3mg/dl, or oliguria with serum creatinine 0-3 with urinary indices indicative of acute renal failure as in the original FACTT trial.

[#] Recommended fluid bolus= 15 mL / kg crystalloid (round to nearest 250 mL) or 1 Unit packed red cells or 25 grams albumin

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

NOTE: For patients without a central venous catheter, no fluid gain over the first 7 study days is recommended once patients' blood pressure has stabilized. Stable blood pressure is defined as no requirement for either vasopressors or a fluid bolus to support blood pressure for 12 or more hours.

E. Adverse Event Reporting and Unanticipated Events

As noted in section 11, investigators will report all adverse events that are serious and study drug or 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 drug or study procedure, as outlined in 21 CFR 312.3 (1), and below. The Medical Monitor will be unblinded and will also determine if the event is unexpected for Acetaminophen. An adverse event is considered "unexpected" if it is not listed in the investigator brochure or 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 a study procedure or the study drug, 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. 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/noticefiles/not99-107.html).

E.1. 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. 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.

E.2. 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 Related”. 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.

E.3. Clinical Outcomes that may be Exempt from Adverse Event Reporting

Study-specific clinical outcomes of sepsis, as outlined in Section 8.1 and 8.3 (Primary and Secondary Outcomes) and Section 7.2 (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 not temporally related to study drug infusion
- Respiratory events: decreased PaO2/FiO2, 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.

F. Alcohol Use Screen Audit C

1. How often do you have a drink containing alcohol?

   ☐ Never (0 points)

   ☐ Monthly or less (1 point)

   ☐ 2-4 times a month (2 points)

   ☐ 2-3 times a week (3 points)

   ☐ 4 or more times a week (4 points)

2. How many standard drinks containing alcohol do you have on a typical day?

   ☐ 1 or 2 (0 points)

   ☐ 3 or 4 (1 point)

   ☐ 5 or 6 (2 points)

   ☐ 7 or 9 (3 points)

   ☐ 10 or more (4 points)

3. How often do you have six or more drinks on one occasion?

   ☐ Never (0 points)

   ☐ Less than monthly (1 point)

   ☐ Monthly (2 points)

   ☐ Weekly (3 points)

   ☐ Daily or almost daily (4 points)

TOTAL POINTS: _____

*If total > 4, patient **is excluded** from the study.*

G. Fever Management Guidelines

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) or Cyclooxygenase-2 inhibitors to treat fever will be strongly discouraged during the 5 day study drug administration and the use of these medications for other indications will also be discouraged. No restriction will be placed on the use of aspirin in doses of less than or equal to 325 mg per day. The use of open-label acetaminophen will not be permitted while receiving study medication. Once the course of study drug administration has been completed, open-label acetaminophen can be administered at the discretion of the treating clinician. Physical cooling will be used at the discretion of the clinical team per local practice preferences (modified from Reference 29).

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