# A Randomized Controlled Pilot Trial of Angiotensin II Versus Vasopressin as Second-line Vasopressor in the Treatment of Septic Shock

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# PROTOCOL TITLE:

A randomized controlled pilot trial of angiotensin II versus vasopressin as second-line vasopressor in the treatment of septic shock

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# REGULATORY FRAMEWORK:

Please indicate all that apply (please note that the regulatory framework **does not** mean the funding source):

| | |
|---|---|
| ☐ | DOD (Department of Defense) |
| ☐ | DOE (Department of Energy) |
| ☐ | DOJ (Department of Justice) |
| ☐ | ED (Department of Education) |
| ☐ | EPA (Environmental Protection Agency) |
| ☒ | FDA (Food and Drug Administration) |
| ☒ | HHS (Department of Health and Human Services) |
| ☐ | VA |
| ☐ | Other: |

**FUNDING:** We are applying for a UNM HSC CTSC Translational and Clinical Pilot Project Award to fund all the study coordination costs (and, as remaining funds allow, the pilot grant will also cover some of the cost of blood sample processing). The company

which manufactures angiotensin II, La Jolla Pharmaceutical Company (LJPC), will provide the supply of angiotensin II to be used at UNMH and funding for local renin testing (both the costs of the renin assays and additional blood processing costs not covered by the pilot grant).

## CLINICAL TRIALS

Is this a clinical trial per the NIH definition of a Clinical Trial? ☒ Yes ☐ No
NIH Definition of a Clinical Trial:

"A research study in which one or more human subjects are prospectively assigned to one or more interventions. An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

**Use the following four questions to determine the difference between a clinical study and a clinical trial:**

1) Does the study involve human participants? ☒ Yes ☐ No
2) Are the participants prospectively assigned to an intervention? ☒ Yes ☐ No
3) Is the study designed to evaluate the effect of the intervention on the participants? ☒ Yes ☐ No
4) Is the effect being evaluated a health-related biomedical or behavioral outcome? ☒ Yes ☐ No

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

If yes to all 4 questions, please confirm that the research team is familiar with and agrees to comply with the investigator requirement to register the study on the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database ☒ Yes ☐ No

For any assistance with registration of your trial or the requirements, please contact HSC-CTSCResearchConcierge@salud.unm.edu.

## Table of Contents

# 1. Objectives

1.1. Our primary objective is to demonstrate that the use of angiotensin II as a second-line vasopressor is non-inferior to vasopressin in the treatment of septic shock with persistent hypotension despite moderate-to-high doses of norepinephrine.

1.2. Our primary hypothesis is that angiotensin II is a safe and effective vasopressor to be used as a second-line agent in patients with septic shock with persistent hypotension despite the use of a moderate-to-high dose of norepinephrine.

1.3. As a pilot study, a major secondary objective will be to demonstrate the feasibility of a randomized controlled trial (RCT) comparing the use of these two vasopressors as second-line therapy in septic shock.

1.4. Our secondary hypotheses are that angiotensin II may be particularly effective in specific subgroups of patients with septic shock. While other specific populations may be determined, some have already been suggested by analyses of ATHOS-3 data. As outlined in further detail below, angiotensin II may benefit patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) or acute respiratory distress syndrome (ARDS). In addition, preliminary data suggest that angiotensin II may specifically be useful in patients with septic shock and high renin levels. While our ability to test these secondary hypotheses will be limited in this pilot RCT, we ultimately aim to clarify if these subgroups or additional subgroups specifically benefit from angiotensin II therapy.

# 2. Background

2.1. Introduction to Angiotensin II

Angiotensin II (Giapreza) was approved by the FDA in 2017 for the treatment of septic or other vasodilatory shock after validation of its use in the ATHOS-3 trial [Khanna et al., *NEJM* 2017; 377:419-30]. The primary benefit of angiotensin II as a vasoconstrictive agent in the treatment of vasodilatory shock likely stems from having a different mechanism than either vasopressin or the various adrenergic agents. Similar to vasopressin when added to norepinephrine, angiotensin II in the ATHOS-3 trial was found to effectively increase BP and reduce the need for other vasopressor agents (with 97% of patients in the trial on norepinephrine and 67% of the patients on vasopressin at the time of randomization) without any significant adverse effects. Though the trial was not powered to evaluate mortality, angiotensin II was associated with a non-significant trend towards decreased overall mortality, a trend which was statistically significant in a subgroup analysis of the sickest patients (i.e., those with APACHE II scores >30).

Despite these promising findings indicating that angiotensin II is effective and safe for the treatment of septic shock, additional data are needed to better define the ideal use of angiotensin II relative to other available agents.

2.2. Current state of vasopressor therapy for septic shock

Norepinephrine and vasopressin are currently the only two vasoconstrictive agents recommended for use in septic shock by the 2016 Surviving Sepsis Campaign (SSC) Guidelines with at least moderate quality of evidence. Of note, these two agents are recommended despite limited mortality data supporting their use, given the inherent difficulty in demonstrating mortality benefit in trials of septic shock (with the mortality benefit of norepinephrine being evident primarily in meta-analyses rather than individual trials; in the case of vasopressin, mortality benefit is not evident in either individual trials or in meta-analyses). In patients who have persistent hypotension despite norepinephrine and vasopressin, the SSC guidelines suggest the use of epinephrine with a "weak recommendation" based on "low quality of evidence." However, the data to support epinephrine as a third-line vasopressor in septic shock are even more limited, consisting of only small trials and meta-analyses which have not detected any mortality benefit relative to other vasopressor agents.

Given that none of the currently used or recommended vasopressor agents used to treat septic shock have compelling data on mortality or other meaningful outcomes to support their use, additional data on vasopressor therapy are needed.

2.3. Preliminary data on benefit of angiotensin II in defined subsets of patients with septic shock

In a post-hoc subgroup analysis of patients with AKI requiring RRT at randomization [Tumlin et al., *Crit Care Med* 2018; 46:949-957], angiotensin II produced a statistically significant benefit in mortality and in the rate of AKI resolution to dialysis-independence, an effect felt to reflect its ability to increase or preserve GFR by causing vasoconstriction preferentially of the efferent renal arteriole (in contrast to most other known endogenous or exogenous vasoconstrictive agents, such as norepinephrine, which act primarily at the afferent arteriole). Notably, while vasopressin also appears to act preferentially on the efferent renal arteriole and was felt to potentially have promise in improving renal outcomes in patients with septic shock, ultimately this benefit was not found when rigorously studied as the primary endpoint of the VANISH RCT published in 2016 [Gordon et al., *JAMA* 2016 Aug 2;316(5):509-18].

In another post-hoc analysis of ATHOS-3 [Busse et al. *Crit Care* 2018; 22(Suppl 1):P125], there was a trend towards decreased mortality with

angiotensin II among patients with ARDS. Such a benefit in ARDS is biologically plausible given that angiotensin-converting enzyme (ACE) is present at high levels in the pulmonary vascular endothelium and therefore ARDS patients with septic shock may be particularly deficient in angiotensin II.

Finally, angiotensin II may be particularly effective in the treatment of septic shock accompanied by elevated renin levels. It is proposed that the endothelial injury associated with septic shock may disrupt the function of the endothelial membrane-bound enzyme ACE, resulting in a state of angiotensin II deficiency in septic shock and, through disruption of negative feedback, elevated renin levels. Recently, a group of investigators (unaffiliated with the development of angiotensin II as a pharmaceutical agent) studied the prognostic significance of renin levels in a mixed ICU population of 112 patients [Gleeson et al., *Crit Care Med* 2019 Feb;47(2):152-158]. They found a statistically significant relationship between renin levels and ICU mortality. Specifically, renin levels outperformed lactate as a prognostic tool in critically ill patients, predicting ICU mortality with a receiver operator curve area under the curve of 0.80. Subsequently, a post-hoc analysis of the ATHOS-3 data was undertaken to analyze the effect of angiotensin II when stratified by renin levels [Bellomo et al. *Am J Respir Crit Care Med* 2020 Nov 1;202(9):1253-1261]. The investigators found that, in patients with renin concentrations above the median, angiotensin II significantly reduced 28-day mortality by over 15% ($p = 0.012$).

## 3. Study Design

3.1. This trial will be a randomized controlled single-center pilot trial. Given differences in the dosing regimens of two vasopressor agents being studied (namely vasopressin being used typically in septic shock at a fixed dose, whereas angiotensin II has been developed and approved as a titratable agent), this will be an unblinded study.

## 4. Inclusion and Exclusion Criteria

4.1. Potential subjects will be identified by regular review of the inpatient ICU census at UNM Hospital.

4.2. Inclusion Criteria:

4.2.1. Adult patients ≥18 years-old with vasodilatory shock refractory to norepinephrine monotherapy, defined as those who require ≥0.2 mcg/kg/min to maintain a MAP between 65-70 mmHg. Patients will be screened once they require ≥0.1 mcg/kg/min of norepinephrine and, if eligible, may be consented at this point. Study drug (angiotensin II or vasopressin) will be initiated once norepinephrine dose reaches ≥0.2 mcg/kg/min for at least 30 minutes.

4.2.2. Patients are required to have central venous and arterial catheters present, and they are expected to remain in place for at least the initial 72 hours of study.
4.2.3. Patients are required to have an indwelling urinary catheter present, and it is expected to remain in place for at least the 72 hours of study.
4.2.4. Patients must have received 20-30 mL/kg of crystalloid over the previous 24-hour period, as clinically appropriate, and no longer be fluid responsive as per UNMH protocol. By UNMH protocol, lack of fluid responsiveness is considered a failure to increase stroke volume, stroke volume index, cardiac output, or cardiac index (typically measured by non-calibrated pulse contour analysis using a FloTrac device) by at least 10% after a 500-mL crystalloid bolus or a passive leg raise. Patients for whom the treating physicians feel that 20 mL/kg of crystalloid may be clinically inappropriate can qualify for the study if the reason for withholding further IV fluids is documented.
4.2.5. Patient or (in patients unable to consent) legal authorized representative (LAR) is willing and able to provide written informed consent and comply with all protocol requirements.
4.2.6. Approval from the attending physician and clinical pharmacist conducting the study.

4.3. Exclusion Criteria:
4.3.1. Patients who are < 18 years of age.
4.3.2. Patients diagnosed with acute occlusive coronary syndrome requiring intervention and/or cardiogenic shock.
4.3.3. Patients with or suspected to have abdominal aortic aneurysm or aortic dissection.
4.3.4. Acute stroke.
4.3.5. Patients with acute mesenteric ischemia or those with a history of mesenteric ischemia.
4.3.6. Patients with known Raynaud's phenomenon, systemic sclerosis, or vasospastic disease.
4.3.7. Patients on veno-arterial (VA) ECMO.
4.3.8. Patients with liver failure with a Model for End-Stage Liver Disease (MELD) score of ≥30.
4.3.9. Patients with burns covering >20% of total body surface area.
4.3.10. Patients with a history of asthma or COPD with active acute bronchospasm or (if not mechanically ventilated) with an acute exacerbation of their asthma/COPD requiring the use of inhaled bronchodilators.
4.3.11. Patients requiring more than 500 mg daily of hydrocortisone or equivalent glucocorticoid medication as a standing dose.
4.3.12. Patients with an absolute neutrophil count (ANC) of < 1,000/$mm^3$.
4.3.13. Patients with hemorrhagic shock OR active bleeding AND an anticipated need (within 48 hours of initiation of the study) for transfusion of >4 units of packed red blood cells.

4.3.14. Patients with active bleeding AND hemoglobin < 7g/dL or any other condition that would contraindicate serial blood sampling.
4.3.15. Untreated venous thromboembolism (VTE) or inability to tolerate pharmacologic VTE prophylaxis.
4.3.16. Patients with a known allergy to mannitol.
4.3.17. Patients with an expected survival of <24 hours, SOFA score ≥ 16, or death deemed to be imminent or inevitable during the admission
4.3.18. Either the attending physician or patient and/or substitute decision-maker are not committed to all active treatment (e.g., DNR status).
4.3.19. Patients who are known to be pregnant at the time of screening.
4.3.19.1. All women ≤50 years-old will need a negative serum pregnancy test (serum quantitative beta-hCG) to enroll.
4.3.20. Prisoner status
4.3.21. Patients who are current participating in another interventional clinical trial.

## 5. Number of Subjects

5.1. As a pilot trial, the size of our trial will be dictated primarily by resources rather than power calculations. Based on these limitations, we plan to enroll 20 subjects to each treatment arm (40 total). However, the subsequent power analysis is included to illustrate the statistical power of the planned trial. Because of the pilot nature of the trial, we will compare the outcomes in each arm using a non-inferiority analysis [Blackwelder, *Control Clin Trials* 1982;3:345-53]. As outlined in the protocol below, we will consent patients before they initiate treatment and we anticipate that another 20-40 patients will be consented but will not be treated with study drug (for total of 60-80 total consented).

5.2. Power Analysis: We hypothesize that angiotensin II will be somewhat (20%) more effective than vasopressin at achieving the primary endpoint, the binary outcome of achieving BP goal or not at 3 hours. Based on ATHOS-3 data (in which a 70% response rate was seen in the angiotensin II arm, which included primarily patients that were treated with norepinephrine, vasopressin, and angiotensin II), we estimate the response rates will be approximately 65% and 45% in angiotensin II and vasopressin arms, respectively, of our trial. We will consider our non-inferiority limit to be a 20% difference between angiotensin II and vasopressin. We will aim for an alpha of 0.05 (one-sided confidence interval) and a power (1-beta) of 0.8. Under these conditions and suppositions, 38 subjects would be required to demonstrate the non-inferiority of angiotensin II.

## 6. Study Timelines

6.1. Each patient will be followed for the duration of their hospitalization.
6.2. We anticipate enrolling patients in this trial at UNMH over 12 months. We anticipate the analyses will take place over a subsequent 6 months. However,

these data may be used in aggregate for further future analyses. The possibility of use of data in future unspecified studies is explicitly included in the consent.

## 7. Study Endpoints:

7.1. Primary Endpoint: Demonstration that the use of angiotensin II as a second-line vasopressor is non-inferior to vasopressin at maintaining MAP ≥65 mmHg in patients with septic shock and persistent hypotension despite moderate-to-high doses of norepinephrine. Our primary endpoint will be assessed at 3 hours.

- 7.1.1. Failure to respond to study drug will defined as any of the following:
  - 7.1.1.1. MAP <65 mmHg at 3 hours
  - 7.1.1.2. Need for increase in background norepinephrine to >0.2 mcg/kg/min despite the addition of the study drug
  - 7.1.1.3. Need for a third vasopressor.

7.2. Secondary Endpoints:

- 7.2.1. The primary endpoint will be re-assessed at multiple additional time points (1 hour, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours)
- 7.2.2. Time to sustained shock reversal (vasopressor independence)
- 7.2.3. Change in catecholamine dose (as quantified in norepinephrine equivalents) at 1 hour, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours.
- 7.2.4. Change in Sequential Organ Failure Assessment (SOFA) scores and/or organ-specific SOFA sub-scores at 1 hour, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours.
- 7.2.5. Frequency of AKI (as defined by KDIGO criteria)
- 7.2.6. Days free from RRT (in first 28 days post study drug initiation)
- 7.2.7. Days free from invasive mechanical ventilation (in first 28 days post drug initiation)
- 7.2.8. ICU length of stay
- 7.2.9. Hospital length of stay
- 7.2.10. ICU mortality (defined as binary yes/no, until ICU discharge or 28 days from drug initiation)
- 7.2.11. Hospital mortality (defined as binary yes/no, until hospital discharge or 28 days from drug initiation)
- 7.2.12. Renin levels [obtained at 4 times points, consent/pre-baseline, baseline/time 0 (drug initiation); 1 hour post-initiation, and 3 hours post-initiation] and differences in the primary and secondary outcomes as stratified by renin levels and/or changes in renin level.
- 7.2.13. Subgroup analyses aimed at identifying clinical syndromes (e.g., septic shock complicated by AKI or ARDS, higher or lower

disease severity) that may specifically benefit from angiotensin II.

7.3. Safety Endpoints/Adverse Events (AEs):

7.3.1. New VTE or arterial thrombosis diagnosed during hospital stay.
7.3.2. Atrial fibrillation
7.3.3. Tachycardia
7.3.4. Lactic acidosis
7.3.5. Peripheral limb/digit ischemia
7.3.6. Intestinal ischemia
7.3.7. Thrombocytopenia
7.3.8. Hyperglycemia
7.3.9. Confirmed infection (with infecting organism confirmed by culture or other identification method; administration of appropriate antibiotic therapy; and clinical documentation of infection)
7.3.10. Any other potentially related AEs will be recorded
7.3.11. For these to be considered AEs, they must be *new* hospital-acquired events which developed *after* randomization.
7.3.12. AE monitoring will occur for up to 28 days or until hospital discharge.

## 8. Research Setting

8.1. The study will be carried out in the adult ICUs at UNMH. The patients will be selected from the various adult ICU services at UNMH (namely, the medical, trauma-surgical, cardiothoracic-vascular, and neuroscience ICU services).

8.2. Patients will be identified from the various ICU team census lists available in PowerChart.

8.3. The only dedicated testing carried out for this trial will be renin assays. The renin levels will be performed by the CTSC Translational Laboratory (T-laboratory) and will be paid for by the study sponsor (with the cost of blood sample processing split between remaining pilot grant funds and the sponsor).

## 9. Resources Available

9.1. Dr. Nathan Nielsen (co-PI) is an Associate Professor of Medicine at UNM in the Division of Pulmonary, Critical Care, and Sleep Medicine and serves as a medical ICU attending at UNM Hospital. He is board-certified in internal medicine, critical care medicine, and blood banking/transfusion medicine. He has published dozens of original research articles, review articles, and abstracts/posters/presentations in the field of critical care, including multiple publications on the treatment of septic shock and specifically on vasopressor therapy and blood pressure goals in septic shock. He is an international expert on the treatment of septic shock, serving as a course content editor,

section editor, master class leader, and lecturer on a variety of sepsis-related topics for the European Society of Intensive Care Medicine (ESICM) LIVES (annual conference) and the ESICM Academy. He is an International Representative for North America for the Council of the ESICM and a Fellow (FCCM) of the U.S.-based Society of Critical Care Medicine (SCCM).

9.2. Dr. J. Pedro Teixeira (co-PI) is an Assistant Professor of Medicine at UNM in the Divisions of Nephrology and Pulmonary, Critical Care, and Sleep Medicine. He is fellowship trained nephrology and critical care medicine and board-certified in internal medicine, nephrology, and critical care medicine. His research interests lie in the realm of AKI, with prior scholarly work focused on the non-traditional systemic effects of AKI as a possible explanation for the high mortality of AKI in the ICU. Since joining the faculty at UNM two years ago, he has been working with Dr. Nielsen and other colleagues to build a local critical care nephrology research program here and is the site PI or co-I on multiple local and multi-center trials of therapies and observational studies in the realm of AKI, sepsis-associated AKI, and COVID-associated AKI that are currently active at UNMH or are due to launch in the near future.

9.3. Dr. Perez Ingles (sub-investigator) is a Pulmonary/Critical Care fellow at UNM. He is from Cuba and obtained his medical degree in Guantanamo, Cuba, where he graduated first in his class. He underwent internal medicine residency training at Texas Tech University Health Science Center in El Paso, TX, where his projects included development and implementation of a training program in bedside ultrasound for his fellow internal medicine residents. His academic interests include several aspects of critical care medicine and since starting his subspecialty training in 2020 he has worked with Drs. Nielsen and Teixeira on developing a critical care clinical research program at UNM Hospital.

9.4. Preeyaporn Sarangarm BCPS, BCCCP, PharmD (sub-investigator) is the supervising pharmacist overseeing the provision of inpatient pharmacy care in both the Emergency Department and the Adult Intensive Care Units at UNM Hospital. Having specialized training in both emergency medicine and critical care pharmacotherapy, she currently serves as the Emergency Medicine PGY2 Pharmacy Residency Program Director in the UNM College of Pharmacy. An accomplished academic pharmacist, she has experience in critical care and emergency medicine clinical trials. For this pilot, she has assisted in the protocol design and will coordinate with her PharmD colleagues in patient screening and recruitment and in the coordination of drug delivery in the trial.

9.5. Katie Chernoby, PharmD, BCCCP; Nicole Hlavacek, PharmD; Jacob Hurt, PharmD, BCCCP; Victoria Milano, PharmD, BCCCP; Josh Newell, PharmD; and Lauren Schluenz, PharmD (sub-investigators) are all academic pharmacists, with subspecialty training in emergency medicine or critical care pharmacy and expertise in the provision of vasopressor therapy, currently

practicing in the Emergency Department or Adult ICUs at UNM Hospital. As frontline providers in the care of septic shock at UNM Hospital, they will assist in the screening and recruitment of subjects for this trial and liaise with the IDS pharmacists to coordinate study drug administration.

9.6. Data collected from PowerChart will be compiled with the use of REDCap, an electronic resource consisting of a secured database stored on a UNM HSC network drive.

9.7. There are 72 (or more) adult ICU beds at UNM Hospital and septic shock is among one of the most common admitting diagnoses, especially to the medical ICU service, which routinely has 24-36 patients split between two care teams. Septic shock is among the most common ICU admission diagnoses at UNMH.

9.8. UNM Clinical and Translational Science Center (CTSC) will be used to provide coordinator support for this study. As a member of the national NIH CTSA Consortium, the UNM CTSC comprises a team of more than 300 investigators and support professionals and serves as a regional leader in biomedical research.

9.9. The following CTSC staff members will provide research coordinator support: Marija Zimkute, Amy Cunningham, and Juan Ceniceros.

9.10. The CTSC T-Laboratory will be used to perform renin assays. The T-Laboratory is comprised of 6,000 gross square feet of wet-lab space located in the UNM CTSC Building. The T-Laboratory offers state-of-the-art equipment and technical assistance with laboratory techniques for UNM HSC investigators. The blood sample processing and renin assays will be performed by research scientist and CTSC laboratory manager Debbie Lovato.

## 10. Prior Approvals

10.1. The inclusion of angiotensin II in the "REFRACTORY SHOCK OPTIONAL TREATMENTS" order set and an angiotensin II titration guideline were approved by the UNMH Critical Care Committee (CCC) on 3/20/20. However, for the duration of this study, though it is listed in this guideline for informational purposes, angiotensin II will not be added as an available order in this PowerChart order set.

10.2. During the April 16, 2020 P&T committee meeting, the UNMH Pharmacy approved the addition of angiotensin II to the UNMH Critical Care Formulary, with a specific plan to introduce initially on limited basis through a research-only protocol.

## 11. Multi-Site Research

N/A.

## 12. Study Procedures

12.1. **Overview**:

12.1.1. This is a single-center, open-label pragmatic randomized controlled pilot trial.

12.1.2. Adult patients with septic shock and persistent hypotension despite moderate-to-high dose of norepinephrine who are hospitalized at a UNMH ICU will be eligible for screening.

12.1.3. We plan to enroll 20 patients in each treatment arm of the trial. Specifically, we hope to have 20 patients in each arm that initiate study drug which, as outlined below, will require more than 40 patients to be consented and randomized (estimated total of 60, but allowing for up to 80).

12.1.4. In the intervention arm, the second vasopressor added to norepinephrine will be open-label titratable angiotensin II; in the other (control) arm the second vasopressor added to norepinephrine will be open-label fixed-dose vasopressin.

12.1.5. For this trial, angiotensin II will be shipped directly by the sponsor to the UNMH IDS pharmacy where it will be stored and prepared for the study subjects allocated to the intervention arm. The sponsor will pay for the angiotensin II used in this study. A dedicated PowerChart research order set specific to this trial will be created to allow for angiotensin II to be ordered by and only by IDS pharmacists for those patients that are randomly allocated to the angiotensin II arm. This will ensure that angiotensin II is only provided to patients as part of the trial and that the trial subjects are not billed for the cost of angiotensin II.

12.1.6. For research purposes, we will be collecting serial blood samples for dedicated renin testing. For renin testing, 2-mL samples of blood will be collected (preferentially from an arterial catheter, whenever feasible) in an EDTA (lavender top) tube after the subjects have been recumbent for at least 30 minutes.

12.1.7. We will clinically assess subjects daily during the treatment phase of the trial for AEs. Otherwise, as this is a pragmatic trial, all data collected (e.g., baseline characteristics, labs, exam findings, concurrent treatments, and outcomes; see above and Data Collection Form for details) will be obtained as SOC in the ICU and prospectively collected from the EMR. Apart from the renin assays, no testing will be done as part of the research protocol.

12.1.8. The study will be conducted in 3 phases, a screening phase (-48h to drug initiation/time 0) and 2 study phases, a treatment phase (time 0 to 72h) and a follow-up phase (72h to hospital discharge) (Figure 1).

12.2. Phase I (screening, -48h to 0)

12.2.1. Patients will be screened by study staff to determine eligibility through review of the census for each of the ICU services at UNMH available in the EMR (PowerChart).

12.2.2. Patients will screen positive once they require norepinephrine at a dose of at least 0.1 mcg/kg/min and they otherwise meet all inclusion and exclusion criteria.

12.2.3. Following screening and determination of eligibility, patients or their LAR may be approached for consent.

12.2.4. If consent is provided, the patients will be randomized to receive angiotensin II or vasopressin infusion. However, study drug (angiotensin II or vasopressin) will not be initiated until the patient's dose of norepinephrine reaches the threshold of 0.2 mcg/kg/min.

12.2.5. Random group allocation will be performed by UNMH IDS pharmacists and therefore completely separated from the investigators recruiting patients for the trial. Prior to trial initiation, the randomization sequence will be generated using the RAND() function within Microsoft Excel software program. Given some patients will be randomized who do not progress to needing a second vasopressor (and therefore will not enter the treatment phase of the trial), the randomization sequence will include 80 patients. Randomization will be done in blocks of 10 to maintain a similar number of subjects in each arm. The randomization sequence file will be kept by the IDS pharmacy, it will be password protected, and the clinical investigators will not have access to it. The IDS will build a data-collection forms that will be maintained over the life of the study, using the Vestigo® research-pharmacy system for recordkeeping and reporting. Once an individual subject/LAR consents to the trial, the investigator will contact the IDS pharmacist who will be responsible for accessing the randomization scheme and then reporting the group assignment (angiotensin II or vasopressin) to the investigator. Randomization will be done once a consented patient reaches a dose of 0.15 mcg/kg/min of norepinephrine monotherapy. Randomization, for patients allocated to the angiotensin II (intervention) arm, will trigger preparation of study drug (angiotensin II) by the IDS pharmacist. For patients allocated to the vasopressin (control) arm, pharmacy, clinical team, or study team will place the order for vasopressin using or local SOC PowerChart order set ("Adult Vasopressors / Inotropes Meds").

12.2.6. At consent and again at drug initiation, blood will be collected for a pre-baseline and baseline renin levels.

12.2.7. All other baseline data (including baseline characteristics, outpatient medications, comorbidities, and past medical history as well as baseline laboratory values, hemodynamic measures, vital signs, other exam findings, concurrent medications, and other treatments) will be obtained as available from the EMR as part of SOC.

12.3. Phase II (treatment, time 0 to 72 hours)

12.3.1. Phase II (time 0) will begin with the initiation of angiotensin II or vasopressin.

12.3.2. Patients who enter the treatment phase of the trial will be those that require ≥0.2 mcg/kg/min of norepinephrine monotherapy to achieve a MAP goal of ≥65 mmHg. The goal will be, with addition of the second vasopressor, to achieve a MAP of ≥65 mmHg by the 3-hour time point. Achievement or not of this MAP goal at 3 hours will be the primary binary endpoint.

12.3.3. In the intervention group, angiotensin II will be started at a dose of 20 ng/kg/min (recommended starting dose in package insert). Thereafter, angiotensin II and norepinephrine will both be titrated according to the schema in Table 1 and according to the UNM Hospitals Nursing Department Titration Guideline approved by the CCC (attached).

12.3.4. In the control group, vasopressin will be used at a fixed dose of 0.04 units/min and norepinephrine will be titrated per usual SOC (as also outlined in the Nursing Department Titration Guideline).

12.3.5. In both the angiotensin II and vasopressin arms of the study, a MAP goal of ≥65 mmHg will be required during phase II.

12.3.6. If a third vasopressor is required to maintain MAP goal, the ICU team will be responsible for selecting and ordering that agent among the available SOC agents. In that case the patient will be considered a treatment failure at that time point.

12.3.7. For research purposes, additional blood for repeat renin levels will be collected at specified intervals (specifically at drug initiation/time 0, 1 hour post-initiation, and 3 hours post-initiation).

12.3.8. Apart from these renin assays, all outcome data (as outlined above and in the Data Collection Forms) will be prospectively sourced from the EMR, as these measures are routinely obtained as part of SOC in the ICU.

12.3.9. During the treatment phase, the patients will be screened at least daily for AEs. As many of the potential AEs are common complications of critical illness, AEs will include only new hospital-acquired events that developed after randomization. AEs will include DVT, PE, arterial thrombosis, atrial fibrillation, tachycardia (>130/min), lactic acidosis, limb/digit ischemia, intestinal ischemia, thrombocytopenia, hyperglycemia, confirmed infection, or other potentially related event.

12.3.10. If, at any point, the investigator(s) and/or the treating ICU attending believe the patient may be at risk of harm (either due to the development of AEs or for another reason), the trial will be terminated and the reason for trial termination will be documented.

12.4. Phase III (72 hours to discharge):

12.4.1. By 72 hours, the patients in the angiotensin II arm that continue to require >0.2 mcg/kg/min of norepinephrine will have vasopressin (or an alternative SOC vasopressor agent, as selected by the treating ICU team) initiated in order to facilitate rapid weaning off of the angiotensin II.

12.4.2. No additional blood will be collected during this phase.

12.4.3. All additional outcomes data will be obtained from the EMR as part of SOC.

12.4.4. In both the angiotensin II and vasopressin arms, the MAP goal after 72 hours will be dictated by the treating ICU team rather than the research team.

12.5. Both drugs being studied, vasopressin and angiotensin II are FDA-approved for the indication (septic shock) under investigation.

12.6. Renin Testing:

12.6.1. The procedure for blood collection for renin level will be the same at all time points: 2 mL will be collected (from arterial catheter, from central venous catheter, or -- if necessary -- peripheral venipuncture) in a lavender top (EDTA) tube while the patient is supine for at least 30 minutes. The samples will be transported to the CTSC T-Laboratory, centrifuged, and processed for storage at -80C. The samples will later be thawed to perform the renin assays in batches (of ≥30 assays at a time). Renin assays will be performed using Human Renin Quantikine ELISA Kit (R&D Elisa - Cat # DREN00). Though all other test results will be pragmatically obtained from the EMR as part of SOC, renin levels are not a SOC test for septic shock and therefore are experimental for this purpose. No samples will be sent to an outside laboratory facility. The renin assays (both the kits and the processing of blood samples) will be paid for by the sponsor at no cost to the subjects (though surplus CTSC pilot funds that remain after paying for the study coordination costs will be also used, if available, to pay for blood processing costs).

12.6.2. The renin assays will be obtained by the study staff. No order will be placed in PowerChart for renin testing, and patients will not be billed for the renin assays.

## 13. Data Analysis

13.1. As outlined above, the primary outcome, the binary outcome of achievement or not of MAP goal at 3 hours, will be assessed using a non-inferiority analysis (with the non-inferiority limit set to 20% difference between both arms, one-sided alpha of 0.05, and beta of 0.2). The power analysis for this outcome has been outlined above.

13.2. Exploratory analyses of the secondary outcomes and the safety outcomes will be done using logistic regression and linear regression as appropriate for binary and continuous variables, respectively.

13.3. For secondary outcomes of particular interest (key secondary outcomes), including hospital and ICU mortality and need for RRT or mechanical ventilation, multivariate analysis will be carried out to further explore the relationship between the treatment drug and outcomes.

13.4. Finally, (depending on recruitment of sufficient patients) we will carry out subgroup analyses on the primary and the key secondary outcomes in prespecified subgroups (e.g., patients with AKI and ARDS) as well as analyses stratified by baseline renin level and severity of illness (SOFA score).

## 14. Provisions to Monitor the Data to Ensure the Safety of Subjects

14.1. The study is considered more than minimal risk due to the number of blood draws involved. However, because this is a pilot trial comparing two FDA-approved therapies, no separate DSMB or DMC

will be utilized. The primary investigators (J. Pedro Teixeira and Nathan D. Nielsen) will perform data and safety monitoring.

14.2. The patients will be monitored for developments of AEs as listed above in section 7.3 (and as listed on the case report forms). These safety endpoints consist of a variety of known potential complications of vasopressor use as well as all adverse reactions listed in the FDA prescribing information for angiotensin II. The latter adverse reactions consist of AEs that occurred with angiotensin II use during the ATHOS-3 trial at a rate of 4% or more and at a rate of 1.5% or more than in the placebo group. In addition, the patients will be monitored for any anticipated or unanticipated serious AEs, which, as defined by the FDA, include AEs that result in death, which are life-threatening, which require prolongation of hospitalization, or that result in significant disability/incapacity.

14.3. The patients in the study will be assessed for the development of AEs daily for the first 4 days (96h) post-drug initiation (i.e., throughout phase II, the 72-hour treatment phase, and for an additional 24 hours). Thereafter, patients will be assessed every 7-10 days for development of any AEs (on days 11, 18, and 28), up until 28 days or until discharge (whichever is first).

14.4. We plan to perform review of scientific literature and data on the safety of both vasopressin and angiotensin II a minimum of quarterly during the study (4 times during the year-long trial).

14.5. Given this is a pilot trial of two-FDA approved treatments, apart from tabulating the number of probably or definitely related serious AEs, there will be no planned interim analysis (of safety or other outcomes data). As above, the safety endpoints will be compared using logistic regression or linear regression at the end of the trial.

14.6. As the underlying condition being studied (septic shock that persists despite a high dose of norepinephrine) inherently carries a high baseline risk of mortality and morbidity, we will terminate the study only for multiple serious AEs that are probably or definitely related to angiotensin II therapy (which is the intervention arm). Specifically, we will terminate the study after any 4 serious AEs (serious as defined above in part 14.2) that are probably or definitely related to angiotensin II. In addition, we will terminate the study for any two deaths which are definitely related to angiotensin II. We will terminate the studies if, on the basis of the quarterly literature review or any additional data that either PI otherwise learns of, we conclude that the standard of care or clinical equipoise between angiotensin II and vasopressin use have shifted in any way which would make the continued operation of the trial unethical.

14.7. We will report any serious AE that is felt to be probably or definitely due to angiotensin II or vasopressin to the HRRC within 48 hours. In the case of any AE felt to be probably or definitely due to angiotensin II, we will also report the event to the sponsor within 48 hours.

## 15. Withdrawal of Subjects

15.1. Though not anticipated, subjects may be withdrawn from the protocol without their consent at any point when it is felt appropriate by either the study investigators OR the treating critical care attending.

15.2. Subjects or their LAR may withdraw from the protocol at any time by sending a letter to Dr. Nielsen or to Dr. Teixeira. If a research subject is still hospitalized, they can ask any provider to contact a member of the study team, and the study team member will then speak to the research subject and withdraw the subject using the same procedures described in the consent process. However, data and samples already collected will not be destroyed.

## 16. Data Management/Confidentiality

16.1. For this study, patients will be tracked using a UNM REDCap database which is stored on a secured UNM-HSC network drive. The following PHI will be included in this database: subject's name, UNMH room number (at time of enrollment), UNMH medical record number, and date of birth. This database will be used for tracking purposes only. Participant name and other identifying information will be linked to a unique study ID. This study ID will not display any information that can identify the participant.

16.2. All the data collected from the participant will be coded using the participant study ID on the Data Collection Forms (DCFs). The DCFs will be a limited dataset (i.e., devoid of PHI apart from dates of service, specifically admit date, date of discharge, date of death, and/or date of transfer in and out of ICU). The DCFs will be kept in paper form in a locked cabinet and as password protected computer (PDF) files. To allow for statistical analysis, the DCFs will be ultimately uploaded onto an electronic research database in REDCap that will also be a limited data set.

16.3. The tracking list linking participant identifying information to participant study data will be kept on the secure online REDCap database. Only the UNM study team will have access to the tracking list. We will keep the tracking list linking participant identifying information and study data until three years after the end of the research study. This tracking list will only be available to UNM research staff.

16.4. All study data will be stored in secured files maintained on the firewall and password protected UNM HSC servers. Three sets of databases will be utilized and managed, an electronic tracking database (in REDCap), an electronic research database (in REDCap), and a paper research database (consisting of DCFs). The tracking database in UNM REDCap is secure and HIPAA compliant. The tracking database which lists the patient identifiers, will not be part of either research

database; only the PIs and select research staff will have access to the tracking database to protect patient privacy. The tracking database and the two research databases will remain as separate databases but linked by a unique identifier (study ID). Research staff will enter study-related information into the REDCap tracking database, the paper research database (DCFs), and the REDCAP electronic research database.

16.5. Paper documents (DCFs and consent forms) will be maintained in a locked area, and only necessary research personnel will have access to this information. Only the participant ID number will be entered into the paper research database.

16.6. All research reports, articles, and presentations stemming from this research will present only aggregate study findings, and participants will never be identified by name or any other personal identifier.

16.7. All data collected from this study will be retained and stored for a maximum of seven years after closure of the study.

16.8. The data collected will not be publicly available.

16.9. The data collected will not include sensitive material (such as HIV status, genetic test results, mental health information, substance abuse information, or criminal records).

## 17. Data and Specimen Banking

N/A. No data or specimens will be banked.

## 18. Risks to Subjects

18.1. Though septic shock itself caries significant risk of adverse outcome, the risks to human subjects from participating this study will be minimal since we are performing a pragmatic comparison of two FDA-approved medications being used for the labeled indications. The additional risks incurred by being in this study include the risk related to (1) the screening and consent process, (2) data collection, and (3) blood sampling required to perform renin analyses.

18.2. Potential risks include:

- 18.2.1. Breach of confidentiality from data obtained during the enrollment process or review of clinical charts.
- 18.2.2. In a minority of patients, venipuncture may be required. Venipuncture can cause bruising, bleeding, and mild discomfort. It is infrequently associated with infection.
- 18.2.3. Answering questions (as required during the consent process) may cause stress and/or emotional discomfort to subjects or their LAR.

18.3. Protection against risks:

- 18.3.1. Subject confidentiality will be maintained by the following methods: All records will be kept in a locked file or on secured

electronic databases (REDCap). All data collected on the data collection forms (DCFs) will be limited data set. Clinical information will not be released without written permission from the subject. Access to identified, source records will be limited to the local site principal investigators and study personnel.

18.3.2. Only a limited data set (the electronic research database) will be analyzed.

18.3.3. As the protocol requires subjects to have functional central venous and arterial catheters, blood sampling will not require venipuncture in the vast majority of patients. In a minority of patients, venipuncture may be needed if the catheters are functional enough for study purposes (i.e., to allow for central venous medication administration and blood pressure monitoring, respectively) but do not allow for blood collection. If phlebotomy is required, only adequately trained study personnel or hospital personnel will draw blood. Blood volumes to be obtained fall within OHRP guidelines for minimal risk studies. Alternative procedures are not feasible.

18.3.4. Subjects or LARs that exhibit signs of stress and/or emotional discomfort will not be consented or will be withdrawn from the study.

18.4. Alternative to participation: Subjects who choose not to participate will have their septic shock treated with additional vasopressor agents that are available outside this trial at UNMH (e.g., vasopressin, epinephrine, phenylephrine, dopamine).

## 19. Potential Benefits to Subjects

19.1. Both therapies (angiotensin II and vasopressin) being compared in this trial are FDA-approved and labeled for the condition being treated (septic shock) and are considered standard of care but have never been directly compared before. As such, there are no known immediate potential direct benefits to the patient.

19.2. As outlined above, angiotensin II seems to be an effective and safe therapy for septic shock. Data from the ATHOS-3 trial suggested there may be some benefit (e.g., trend towards decreased mortality) or benefit in particular patient subgroups (e.g., patients with high renin levels or high severity of illness, patients requiring mechanical ventilation or RRT); however, these signals of benefit were all secondary endpoints of the trial and therefore must be interpreted with caution and warrant further study in this and other future trials.

## 20. Recruitment Methods

20.1. The study staff will systematically screen new admissions to the UNMH intensive care units, at an interval of up to once daily and no

less than once weekly, for possible inclusion in the study. Screening will utilize the ICU census available in the UNMH EMR (PowerChart). Using data available in the EMR, study staff will determine if the subjects meet study inclusion and exclusion criteria. Appropriateness of potential subjects will be confirmed by discussion between study staff and the attending intensivist caring for the patient. If they meet all criteria, the patient or LAR will be consented to participate in this study by Dr. Nielsen, Dr. Teixeira, Dr. Perez-Ingles, or ancillary study staff.

20.2. Prior to launch of this study, Drs. Nielsen and/or Teixeira will provide education to other critical care faculty and fellows at UNMH on the clinical use of angiotensin II, either in email form or by presenting at an educational setting such as Pulmonary/Critical Care Division Conference or Journal Club, Surgical-Critical Care Conference or Journal Club, or New Mexico Regional Critical Care Conference.

20.3. As outlined above, the study staff will include multiple PharmDs who will participate in the subject recruitment process. At UNMH, all inpatient pharmacy orders, including vasopressor orders, require pharmacist approval prior to dispensation. As such, the pharmacists in the study trial will be well suited to screen patients for possible inclusion in the study. Though they will participate in screening and assessing inclusion and exclusion criteria, the pharmacists will not participate in the consent process but rather will contact Dr. Nielsen, Dr. Teixeira, Dr. Perez-Ingles, or other ancillary study staff.

## 21. Provisions to Protect the Privacy Interests of Subjects

21.1. To protect privacy interests, it will be explained to each participant that no study participant will be identified by name in any publication, meeting, abstract, or report derived from the study results. Because identifying information will be used in the tracking database, this information will be stored in a secure online database stored on UNM-HSC servers (REDCap). All data compiled on the research database will have all patient identifiers removed and will only have the patient's study number.

21.2. All discussions with patients or their LARs will take place in a private setting (e.g., in their ICU room or by phone in a private setting).

21.3. Study participant confidentiality will be strictly held in trust by all participating investigators and their staff. No information concerning the study or data will be released to any unauthorized third parties without prior approval.

## 22. Economic Burden to Subjects

N/A. There will be no economic burden to subjects.

## 23. Compensation

N/A. There will be no compensation to subjects.

## 24. Compensation for Research-Related Injury

N/A. There will be no compensation for research-related injury. This research involves minimal risk to subjects.

## 25. Consent Process

25.1. An approved member of the study team will conduct the consent process with the participant and/or their LAR in a private area of the hospital or by phone if needed.

25.2. The study team, in consultation with the clinical care provider, will determine if a participant or LAR has capacity to consent. Please see section 25.12.2 below for further details.

25.3. It may not be possible to have an in-person discussion of the study with participants or their LAR. Documenting written informed consent in these instances must involve a process as follows: the participant or their LAR receives a copy of the informed consent document in advance of a telephone discussion. The investigator obtains consent over the telephone with the participant or their LAR.

25.4. The informed consent form may be mailed, emailed, or faxed to the participant or their LAR. The consent discussion may then be conducted by telephone or in person when the subject or subject's LAR can read the consent form during the discussion.

25.5. Investigators will explain the study to the potential participant or their LAR by reading the informed consent document to the participant and/or LAR, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation) and allowing the potential participant or their LAR ample opportunity to ask questions. This can be done by phone or in person.

25.6. Investigators will ensure a thorough verbal discussion by phone or in person of the consent form. Investigators will allow the potential participant or LAR time to read the consent form and allow the participant or their LAR sufficient time to consider whether or not to participate in the research.

25.7. Investigators will ensure the potential participant's or their LAR's additional questions are addressed.

25.8. Participants and/or their LAR will be asked to explain the purpose of the study, procedures involved, and/or conditions for participation to confirm understanding.

25.9. If the participant or LAR agrees to participation, s/he signs the consent form and returns it to the investigator for signature and date. The signed and dated consent form can be returned to investigators by

mail, fax, or by scanning the consent form and returning it through a secure e-mail account.

25.10. Once the signed form is received, the investigator who conducted the informed consent will sign and date the consent and will ensure the participant or their LAR receives a copy of the fully signed consent form. The fully signed original consent form will be filed with the participant's study records.

25.11. Ongoing consent from participants and and/or their LAR will be ascertained as research procedures are being conducted.

25.12. Subjects not fluent in English

25.12.1. Non-English-speaking patients may be included in the study. This will only include Spanish-speaking individuals.

25.12.2. The consent process will be conducted by a member of the study team fluent in the Spanish language and/or with the assistance of a qualified interpreter. The subjects will use a Spanish language consent which will be translated in full from the English language consent by a bilingual study staff member. If the study team member obtaining the consent is bilingual (e.g., Drs. J. Pedro Teixeira or David Perez Ingles), they will obtain consent as above. However, if the person obtaining consent does not speak Spanish, these following elements will apply: 1) A written copy of the translated full Spanish consent document must be provided to the subject. 2) The entire consent process must be witnessed by an individual who is fluent in both English and Spanish. The translator may serve as the witness. 3) The HRRC-approved Spanish version of the consent form must be signed by the investigator (or study staff member) authorized by the HRRC to obtain consent, by the witness to the consent process, and by the subject.

25.12.3. The LAR will be utilized as described in sections 25.1 to 25.10.

25.13. Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

25.13.1. Some participants are expected to be cognitively impaired, either due to a pre-existing condition or because of conditions related to their critical illness. Cognitively impaired participants will be enrolled in the study with the consent of their LAR.

25.13.2. The study team, in consultation with the clinical care provider, will determine if a participant or LAR has capacity to consent. Specifically, the investigators will utilize the Capacity to Consent Quiz and/or the good clinical practice "teach back technique" with the consent form. After the consent form has been discussed with the participant, the investigator will administer the Capacity to Consent Quiz. Based on the results, the investigators will determine if the participant or LAR has the ability to consent.

25.13.3. Capacity to consent will be evaluated by the study team, in consultation with the clinical care provider, as part of the

ongoing consent process as described above. If the participant regains capacity to consent, a member of the study team will conduct the consent process as described above.

25.13.4. We will obtain evidence of agency under a durable power of attorney or surrogate health decision maker status under the NM Uniform Health Care Decisions Act, NMSA 1978, 24-7A-1 et seq.

25.14. Subjects who are not yet adults (infants, children, teenagers): N/A

25.15. Waiver or Alteration of Consent Process: N/A. No waiver of consent will be required. Review of patient records prior to consent will be done only as preparatory to research to allow for screening.

## 26. Documentation of Consent

26.1. For English-speaking participants (or LARs), consent will be documented using an HRRC-approved consent document.

26.2. For Spanish-speaking participants (or LARs), a HRRC-approved full Spanish language translation of the consent will be used to document consent.

## 27. Study Test Results/Incidental Findings

27.1. We will not be sharing individual results or incidental findings with the patients. The bulk of the data being collected will be collected pragmatically from the EMR based on physical exams findings and lab testing that will be carried out and documented as part of routine clinical care. The only additional testing being done will be renin levels, which, in the context of critical care, are exploratory pieces of data that do change standard of care management of septic shock.

## 28. Sharing Study Progress or Results with Subjects

N/A. As a pilot trial, study progress or results will not be shared with subjects.

## 29. Inclusion of Vulnerable Populations

29.1. Cognitively impaired adults will be included in the study since the disease under investigation (septic shock or other vasodilatory shock) disproportionately affects older adults and/or contributes to the temporary cognitive impairment of a significant proportion of patients. To protect their rights and welfare, consent will be sought from competent LARs, and participants who regain capacity to consent as (determined by the study team in consultation with clinical care providers) will be re-consented.

## 30. Community-Based Participatory Research

N/A. There is no community-based participatory research in this protocol.

## 31. Research Involving American Indian/Native Populations

N/A. This protocol involves patients who come to UNM Hospital regardless of ethnicity. American Indian patients who speak English or Spanish may be enrolled.

## 32. Transnational Research

N/A. This protocol does not involve transnational research.

## 33. Drugs or Devices

33.1. This research involves no devices and no investigational drugs.
33.2. See drug attachments for details. Both vasopressin and angiotensin II are FDA-approved drugs that will be used in an on-label fashion to treat septic shock. Though the use of angiotensin II will be at first restricted at UNMH to this protocol, it is not an investigational agent and its storage, handling, and administration will be governed by usual UNMH pharmacy and clinical care policies and procedures for similar agents, including the policies and procedures already approved by the UNMH Critical Care Committee and the UNMH Inpatient Pharmacy.

## 34. Principal Investigator's Assurance

By submitting this study in the Huron IRB system, the principal investigator of this study confirms that:

☒ The information supplied in this form and attachments are complete and correct.

☒ The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☒ Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is for it to be directly entered onto a data collection form that is in a secured access folder on an HS drive behind a firewall, or in a secure UNM Data Security approved system such as RedCap.
2. **Data collection of <u>de-identified data</u>**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be done temporarily using a personal or university owned electronic storage device or hard copy document. **The important security safeguard is that no identifiers be include if the data is entered or stored using an untrusted device or storage.**
3. **Permanent (during data analysis, after study closure**) storage must reside on HSC central IT managed storage. Processing of data (aggregation, etc.) are to be carried out in such a way as to avoid creating/retaining files on untrusted storage devices/computers. Trusted devices are HSC managed and provide one or more of following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.

4. **Alternate storage media** must be approve by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

## 35.CHECKLIST SECTION

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

## 36.Partial Waiver of Consent for Screening/Recruitment

*Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.*

A. Describe the data source that you need to review (e.g., medical records):

N/A. No waiver of consent will be required. Review of patient records prior to consent will be done only as preparatory to research to allow for screening.

B. Describe the purpose for the review (e.g., screening):

C. Describe who will conducting the reviews (e.g., investigators, research staff):

D. Do all persons who will be conducting the reviews already have permitted access to the data source?

☐ Yes

☐ No. Explain:

*i.* Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

*1.* <u>The activity involves no more than minimal risk to the subjects</u> because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

☐True

☐Other justification:

2. <u>The waiver or alteration will not adversely affect the rights and welfare of the subjects</u> because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

☐ True

☐ Other justification:

3. <u>The research could not practicably be carried out without the waiver or alteration</u> because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☐True
☐Other justification:

4. Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*
   ☐True
   ☐Other justification:

## 37.Partial Waiver of HIPAA Authorization for Screening/Recruitment

*Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).*

A. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?
   ☒ Yes. Describe:

   As part of the screening process, the following PHI will be collected in the online secure tracking database (on REDCap):
   Name
   Medical Record Number
   Hospital Room Number (on Date of Study Screening/Entry)
   Date of Birth

   ☐ No

B. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

   We are requesting waiver of HIPAA authorization for screening purposes. Our justification for the request is to be able to determine if patients in the ICU meet eligibility criteria for participation in this trial. Any identifiers collected will be destroyed immediately for participants not interested in study and at end of study for participants who decide to participate.

C. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
   ☒ True
   ☐ False

## 38. Vulnerable Populations (Checklist)

### A. Adults with Cognitive Impairments

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

   Cognitively impaired adults will be included in the study since the disease under investigation (septic shock and critical illness in general) disproportionately affects older adults and/or contributes to the temporary cognitive impairment of a significant proportion of patients. To protect their rights and welfare, consent will be sought from competent LARs and participants who regain capacity to consent (as determined by the study team in consultation with clinical care providers) will be re-consented.

2. Describe how capacity to consent will be evaluated.

   The study team, in consultation with the clinical care provider, will determine if a participant or LAR has capacity to consent. The investigators will use the Capacity to Consent Quiz and/or the good clinical practice "teach back technique" with the consent form. After the consent form has been discussed with the participant, the investigator will administer the Capacity to Consent Quiz. Based on the results, the investigators will determine if the participant or LAR has the ability to consent.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

   Capacity to consent will be evaluated by the study team, in consultation with the clinical care provider, as part of the ongoing consent process as described above. If the participant regains capacity to consent, a member of the study team will conduct the consent process as described above.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

   The study team will utilize the good clinical practice "teach back technique" to provide information about the research to subjects. The subjects will be asked to "teach back" the provided information to the team member for assessment of understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

No, we will only enroll research subjects where consent can be obtained from the subject or the LAR

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

   This trial involves the comparison of two FDA-approved treatments for septic shock and therefore is considered minimal risk. The minimal risks to subjects are reasonable despite lack of known anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

   As outlined above, both treatments being studied, vasopressin and angiotensin II, are FDA-approved for septic shock and seem to be effective and safe therapies. Furthermore, also as previously outlined, data from a prior seminal trial suggest there may be some specific benefits to angiotensin II (e.g., trend towards decreased mortality in patients with high disease severity) and benefit in particular patient subgroups, but these signals of benefit were all secondary endpoints of the trial and therefore must be interpreted with caution and warrant further study in this and other future trials. The only patients being enrolled are those who require vasopressor therapy for septic shock. The two drugs being studied as second-line therapy in this trial appear to be at least as beneficial and safe as the other vasopressor agents available as second-line therapy for septic shock (e.g., epinephrine, phenylephrine, and dopamine).

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

   Well-being of the subjects will be monitored by the treating physicians. Subjects who appear distressed by their participation in the study will be withdrawn by the study team.

## 39.Data Transfer/Sharing (Checklist)

A. Will data be transferred/shared with an external entity (institution, company, etc.)?
   ☐Yes
   ☒No. **The remainder of this section does not apply.**

B. Indicate if the data is incoming and/or outgoing:
C. Provide the name of the entity that data will be transferred/shared with:
D. Provide the contact name, email and phone number with whom data is being transferred/shared with:
E. Who is responsible for transmission of the data?

F. Who is responsible for receiving the data?
G. Describe how the data will be transferred/shared. Please note data cannot be transferred/shared without assistance from UNM HSC IT. **Requesting HSC Central IT Transfer is detailed on the Sponsored Projects website:**
H. For data being transferred/shared with outside locations or entities, describe the following:
    - Where is data storage and how will it be maintained in a secure manner (i.e. encryption, password protection, use of Qualtrics or REDCap, etc)?
    - What is method in which data will be collected and stored (i.e. electronic, hard copy, etc)?
    - How long will the data be stored?
    - Who will have access to data?
I. Please list all specific data elements, variables, etc. to be sent out and/or received. Indicate if the data contains identifiers and health information. Please note that identifiers that MUST be removed to make health information de-identified are as follows: Names, All geographic subdivision smaller than a State, All elements of year (except year), Telephone, Fax numbers, E-mail addresses, Social Security, Medical record number, Health plan beneficiary, Account numbers, Certificate/license numbers, Vehicle identifiers and serial numbers, Device identifiers and serial numbers, Web URLs, IP address numbers, Biometric identifiers, full face photographic images, and Any other unique identifying number, characteristic or code.)
J. If the research requires the access, use, or disclosure of any of the 18 individually identifiable protected health information (PHI) identifiers that can be used to identify, contact, or locate a person (e.g., name, medical record number, etc.), are the subjects going to consent to or authorize the disclosure of their individually identifiable health information?
    a. ***Or*** is HIPAA authorization altered or waived?
K. What is the classification of the data (de-identified, limited data set, protected health information, other).
L. Does the request to transfer/share data include clinical data that belongs to the UNM Health Systems?
M. Does the data to be transferred/shared include information about patients seen at external health system or at a third party medical provider?
N. Is the external entity a "covered entity"?
O. Is the data that is going to be transferred/shared owned or partially owned by another party or have any type of restrictions including regulatory restrictions (i.e. HIPAA, FERPA, etc.)?
P. Is the data publicly available? If yes, please provide details:
Q. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health?

## 40.Specimen Transfer/Sharing (Checklist)

*Provide all requested information if the research involves transferring/sharing of specimens with an external entity (institution, company, etc.).*

A. Will specimens be transferred/shared with an external entity (institution, company, etc.)?

☐Yes
☒No. **The remainder of this section does not apply.**

B. Indicate if the specimens are incoming and/or outgoing:
C. Provide the name of the entity that specimens will be being transferred/shared with:

D. Provide the contact name, email and phone number with whom specimens are being transferred/shared with:
E. Who is responsible for sending out the specimens? Please note specimens cannot be sent out without a fully executed material transfer agreement.
F. Who is responsible for receipt of the specimens? Please note specimens cannot be received without a fully executed material transfer agreement.
G. For specimens being transferred/shared with outside locations or entities, describe the following:
   - *Where is specimen storage and how will it be maintained in a secure manner?*
   - *What is method in which specimens will be collected and stored?*
   - *How long will the specimens be stored?*
   - *Who will have access to the specimens?*