PROTOCOL TITLE:

DPP3, Angiotensin II, and Renin Kinetics in Sepsis (DARK-Sepsis) pilot: serum biomarkers to predict response to angiotensin II versus standard-of-care vasopressor therapy in the treatment of septic shock, a randomized controlled pilot trial

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VERSION NUMBER: 3.2

DATE: 21 January 2026

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)
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☒	FDA (Food and Drug Administration)
☒	HHS (Department of Health and Human Services)
☐	VA
☐	Other:

FUNDING: La Jolla Pharmaceutical Company (LJPC).

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.

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1. Objectives

1.1. Our primary objective is to demonstrate that renin and dipeptidyl peptidase 3 (DPP3), as novel biomarkers, can be used to predict response to angiotensin II in the treatment of septic shock with persistent hypotension despite moderate doses of norepinephrine.

1.2. Our primary hypothesis is that renin and DPP3, obtained relatively early in the course of septic shock, will be useful to predict response specifically to angiotensin II when added to moderate-dose norepinephrine in patients with septic shock. In order to determine the ability of renin and DPP3 to determine the specific response to angiotensin II therapy, we will compare the changes in renin and DPP3 levels in patients treated with angiotensin II to the changes in renin and DPP3 levels observed a control group treated with standard of care vasopressors.

1.3. Our secondary hypothesis is that angiotensin II, when added to moderate doses of norepinephrine relatively early in the course of septic shock, is a safe and effective second-line vasopressor when compared to standard of care.

1.4. An additional secondary hypothesis is that angiotensin II may be particularly effective (compared to standard of care) in other 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), acute respiratory distress syndrome (ARDS), or high severity of illness.

1.5. As a pilot study, a major secondary objective will also be to demonstrate the feasibility of a randomized controlled trial (RCT) comparing the use of angiotensin II to other vasopressor agents using renin and/or DPP3 levels to guide patient selection.

1.6. Finally, various renin assays have been used to carry out similar critical care research, but high-quality data to guide the choice of renin assay is lacking. Among the renin assays that have been utilized, both total renin assays (which measure both active and inactive forms of circulating renin) and assays specific for active renin have been used, though additional data are needed to determine which of these is preferred as a biomarker in septic shock. As such, in this study we will measure both total renin and active renin in order to determine if one assay outperforms the other.

2. Background

2.1. 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.

2.2. 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. In particular, we need additional data to guide the choice of vasopressor therapy among the available options, including adrenergic agents, vasopressin, and angiotensin II.

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.

2.4. Preliminary data suggesting that renin may be a useful biomarker in sepsis and critical illness

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. 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.

The utility of renin levels to predict outcomes in patients with critical illness has been demonstrated in at least three additional prospective studies. Specifically, renin levels or changes in renin level have been shown to predict AKI and AKI-requiring RRT in septic shock (Nguyen et al. *Shock* 2019 Oct;52(4):e22-e30), to predict AKI after cardiac surgery (Küllmar et al. *Am J Respir Crit Care Med 2021* May 1;203(9):1119-1126), to predict death and

major adverse kidney events in a mixed ICU population (Flannery et al. *Crit Care* 2021 Aug 14;25(1):294), and to predict mortality in hypotensive ICU patients (Jeyaraju et al. *Crit Care Med* 2022 Jan 1;50(1):50-60).

2.5. Preliminary data suggesting that renin may be a useful to guide the use of angiotensin II in septic shock

Angiotensin II may be particularly effective in the treatment of septic shock accompanied by elevated renin levels. 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% ($p = 0.012$).

The ability of angiotensin II to influence renin levels was demonstrated by a recent retrospective analysis of 40 patients undergoing cardiac surgery which demonstrated that angiotensin II use (but not norepinephrine alone) resulted lower subsequent renin levels (Meersch et al. *Anesth Analg* 2022 May 1;134(5):1002-1009).

2.6. Preliminary data suggesting that DPP3 may be a useful biomarker in sepsis and critical illness and may identify patients likely to benefit from angiotensin II therapy

Dipeptidyl peptidase 3 (DPP3) is an aminopeptidase that cleaves a variety of biologically active oligopeptides including angiotensin II (Malovan et al., *FEBS J* 2022 Mar 12 [online ahead of print]; Pang et al., *Hypertension* 2016 Sep;68(3):630-41; Prajapati & Chauhan, *FEBS J* 2011 Sep;278(18):3256-76). In animal models, DPP3 has been demonstrated to modulate the renin-angiotensin system (Jha et al., 2020). Specifically, DPP3 cleaves angiotensin II without acting on angiotensin I, leading an elevation in the ratio of angiotensin I/angiotensin II (Jha et al., *J Biol Chem* 2020 Oct 2;295(40):13711-13723). Of note, an elevated ratio of angiotensin I/angiotensin II was observed in patients with catecholamine-resistant septic shock enrolled in the ATHOS-3 trial, and – like elevations in renin level – such as elevated ratio may identify patients likely to benefit from angiotensin II therapy (Bellomo et al., *Crit Care* 2020 Feb 6;24(1):43). Also similar to renin, levels of DPP3 have been found to be elevated in animal models of septic shock (Deniau et al., *PLoS One* 2020 Aug 27;15(8):e0238039) and in human patients with sepsis, especially those with high severity of illness or those who ultimately die from sepsis (Rehfeld et al., *J Appl Lab Med* 2019 May;3(6):943-953).

More recently, in a multicenter observational study of 600 patients with sepsis, DPP3 levels were shown to be associated with development of renal or hepatic dysfunction or the need for RRT, mechanical ventilation, or vasopressor support (Blet et al., *Crit Care* 2021 Feb 15;25(1):61). In addition, DPP3 levels independently predicted short term mortality and – again similar to renin – outperformed lactate in the prediction of short-term mortality. Improvements in DPP3 levels, in contrast, were associated with improving organ function and lower risk of death.

Notably, in animal models of sepsis, inhibition of DPP3 has been shown to improve hemodynamics and improve survival by mitigating septic cardiomyopathy, an effect which may be mediated by the resulting increase in angiotensin II levels (Deniau et al., *PLoS One* 2020 Aug 27;15(8):e0238039). Finally, though additional human data are needed to evaluate this theory, the use of pharmacologic angiotensin II to treat septic shock has been suggested as a potential therapy to specifically overcome the hemodynamic deterioration induced by elevated DPP3 in sepsis (Picod et al., *Am J Respir Crit Care Med* 2021 Feb 15;203(4):526-527).

Collectively, these data strongly suggest that DPP3 – alongside renin – warrants additional prospective study as a biomarker in sepsis and specifically as a biomarker that may identify patients who may benefit from angiotensin II therapy.

2.7. Unanswered questions about the use of renin and DPP3 as biomarkers in septic shock

Given the accumulating data that renin and DPP3 levels may serve as general predictors of outcome of septic shock or critical illness in general, the relationship between renin and DPP3 levels and response to angiotensin II therapy remains unclear. Specifically, given (1) that renin and DPP3 levels are strongly associated with increased risk of death or adverse events in critical illness and (2) that angiotensin II (based on the ATHOS-3 data) may be particularly effective in patients with high severity of illness (e.g., APACHE II >30), it is not clear if renin or DPP3 levels independently predict response to angiotensin II or if the relationships between renin and DPP3 levels and angiotensin II are mediated by underlying severity of illness. In addition, the data linking renin levels to angiotensin II response thus far have all been retrospective. In the case of DPP3, the ability of elevated DPP3 levels to identify patients that may benefit from angiotensin II has only been proposed based on biologic rationale but has not yet been demonstrated.

Furthermore, as several of the above referenced studies (Küllmar et al. *Am J Respir Crit Care Med 2021* May 1;203(9):1119-1126; Jeyaraju et al. *Crit*

Care Med 2022 Jan 1;50(1):50-60; Meersch et al. *Anesth Analg* 2022 May 1;134(5):1002-1009; Blet et al., *Crit Care* 2021 Feb 15;25(1):61) found relationships between *changes* in renin or DPP3 levels and outcomes or angiotensin II response, it is unclear if static baseline renin levels or changes in renin levels are more useful as biomarkers in septic shock.

Finally, little is known about the effect of *stopping* angiotensin II therapy on renin levels. Since elevated renin predicts poor outcome in septic shock and angiotensin II therapy appears to benefit patients with elevated renin and to produce a decrease in renin levels, it is plausible that renin levels may rebound after angiotensin II therapy is stopped. However, such a rebound has never been demonstrated. And, if a rebound effect does exist, it is unknown whether renin elevation in that context carries any prognostic significance. In the case of DPP3, the kinetics of circulating DPP3 levels with either starting or stopping angiotensin II remains unknown.

Therefore, we propose this pilot randomized controlled trial evaluating the use of renin and DPP3 levels to predict response to angiotensin II therapy. We aim to prospectively clarify the relationship between blood levels of renin and DPP3, clinical response to angiotensin II, and severity of illness in patients with septic shock. In order to determine if the ability of renin or DPP3 to predict clinical response to vasopressor therapy is specific to angiotensin II as postulated, we will assess renin and DPP3 levels in patients with septic shock treated with angiotensin II and in a control group not treated with angiotensin II. Because (1) we hypothesize that renin and DPP3 levels will identify patients that specifically benefit from angiotensin and because (2) the need for high doses of catecholamine monotherapy in septic shock is consistently associated with high mortality (Bassi et al. *Crit Care Res Pract* 2013;2013:654708), we will be introducing angiotensin II therapy somewhat earlier than previously done in prior trials. To shed light on the relationship between angiotensin II response, overall outcome, levels of renin and DPP3, and *changes* in levels of renin and DPP3, we will collect renin and DPP3 levels at multiple time points in both patients treated with angiotensin II and those treated with other vasopressors. Finally, to investigate if renin or DPP3 rebound occurs after angiotensin II discontinuation and if such a rebound carries any prognostic significance, we will obtain levels of renin and DPP3 after study drug discontinuation in patients treated with angiotensin II.

3. Study Design

3.1. This trial will be a randomized controlled single-center pilot trial. Given our investigational product (IP), angiotensin II, will be compared to the standard of care (SOC), 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 persistent vasodilatory shock despite moderate-dose vasopressor therapy, defined as those who require norepinephrine or other vasopressor therapy with norepinephrine equivalent dose (NED) at ≥0.1 mcg/kg/min for at least 30 minutes to maintain a MAP between 65-70 mmHg. [NED is defined in the ATHOS-3 trial and elsewhere (e.g., Jentzer et al. *Chest* 2018 Aug;154:416-426).]

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 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.

4.2.4. 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.

4.2.5. 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. Comfort measures status (limitations such as DNR or DNI status permitted if the patient is otherwise pursuing life-prolonging therapies)

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 currently participating in another interventional clinical trial.

4.4. The following patients will be excluded post-randomization prior to study hour 0 (i.e., between the pre-baseline and baseline time points):

4.4.1. Patients are fully weaned off vasopressors in the interim

4.4.2. Patients who develop or are discovered to have an exclusion criterion that was not present or known to the investigators at the time of consent or randomization.

5. Number of Subjects

5.1. As previously indicated, we will be assessing the ability of baseline biomarker levels to predict response to angiotensin II therapy (quantified, as outlined in further detail below, by assessing doses of background vasopressors and total vasopressors). As outlined in more detail below, we will perform multiple regression analysis to assess this relationship between levels of total renin, active renin, and DPP3 and vasopressor response. The primary analysis will include three multiple regression analyses – one analysis each for total renin, active renin, and DPP3 – of the two predictor variables of (1) baseline levels of total renin, active renin, or DPP3 and (2) treatment group (angiotensin II vs. standard of care) to predict vasopressor response. In this instance with 2 predictor variables, if aiming for a power (1-beta) of 0.8 and significance level (alpha) of 0.05, a sample size of 31 would be required to detect a relatively large effect size (i.e., f^2 of 0.35). If including baseline level of each biomarker, treatment group, and severity of illness (i.e., SOFA score) as 3

predictor variables, a sample size of 36 would be required to detect a similar effect size.

5.2. We will plan to randomize 40 patients.

5.3. If patients are excluded post-randomization, we will randomize additional subjects as needed to ensure that 40 patients are both randomized and initiate the study. We anticipate that 5 or fewer patients will be excluded post-randomization (i.e., that 45 or fewer total subjects will need to be randomized to ensure our target sample size of 40 patients).

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 6 months. We anticipate the analyses will take place over a subsequent 6 to 12 months.

7. Study Endpoints:

7.1. Primary Outcome: Demonstration that baseline levels of total renin, active renin, and/or DPP3 are useful in predicting the response to angiotensin II when added to moderate-dose norepinephrine monotherapy. In this protocol, the term "biomarker" will be used hereafter to refer to levels of total renin, active renin, and DPP3.

7.1.1. To assess this primary outcome, we will define a **primary proximate endpoint** as response to vasopressor therapy at 3 hours post-drug initiation in the angiotensin II arm and at the equivalent time point in the standard of care arm.

7.1.1.1. Response to angiotensin II will be assessed at 3 hours post-drug initiation and will be defined as reduction in dose of background vasopressor therapy as measured by NED.

7.1.1.2. In order to determine if biomarkers specifically predict response to angiotensin II (rather than vasopressor therapy in general), we will also determine the ability of biomarkers to predict total vasopressor requirement by NED in the SOC group at the equivalent baseline time point (see Table 2, Biomarker Assay Schedule).

7.1.2. In order to assess the effectiveness of baseline biomarker levels to predict response to angiotensin II versus SOC vasopressors, biomarker levels will be obtained at drug initiation in the angiotensin II arm and at the equivalent time point in the SOC arm. For purposes of clarity, we will consider the levels of our biomarkers, total renin, active renin, and DPP3, our **major intermediary endpoints**.

7.1.3. In order to assess the influence of severity of illness on the relationship between baseline biomarker levels and vasopressor response, SOFA score will be tabulated at baseline (drug initiation in the angiotensin II arm and equivalent time point in

the SOC arm). SOFA score will be considered **our primary co-variable**.

7.2. Secondary Endpoints:

7.2.1. The primary proximate endpoint (vasopressor response, as quantified by decrease in NED of background vasopressor(s) in the angiotensin II arm and total vasopressor requirement in NED in the SOC arm) 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 Sequential Organ Failure Assessment (SOFA) scores and/or organ-specific SOFA sub-scores at 24 hours, 48 hours, and 72 hours.

7.2.4. Frequency of AKI (as defined by KDIGO criteria)

7.2.5. Days free from RRT (in first 28 days post-randomization)

7.2.6. Days free from invasive mechanical ventilation (in first 28 days post-randomization)

7.2.7. ICU length of stay

7.2.8. Hospital length of stay

7.2.9. ICU mortality (defined as binary yes/no, until ICU discharge or 28 days from randomization)

7.2.10. Hospital mortality (defined as binary yes/no, until hospital discharge or 28 days from randomization)

7.2.11. The following will be defined as secondary endpoints of particular interest (key secondary outcomes):

7.2.11.1. Days free from RRT (up to 28 days)

7.2.11.2. Days free from mechanical ventilation (up to 28 days)

7.2.11.3. ICU mortality (up to 28 days)

7.2.11.4. Hospital mortality (up to 28 days)

7.2.12. While the biomarker levels obtained immediately before angiotensin II initiation is mechanistically the best choice of baseline when assessing drug response, the ultimate hypothesis is that biomarkers levels early in the course of septic shock may be useful to direct the early selection of vasopressors. As such, we will also obtain *pre-baseline* biomarker levels immediately upon patient entry into the study.

7.2.13. As previously outlined, it is unclear if static baseline total renin, active renin, or DPP3 levels or changes in these levels are superior when using these substances as biomarkers in sepsis. Therefore, we will explore the relationship between *changes* in biomarker levels and response to angiotensin II vs. SOC by obtaining biomarker levels at multiple additional time points. To facilitate direct comparison between the two groups, we created a Biomarker Assay Schedule (Table 2) based on the estimation that study drug initiation in the angiotensin II arm will occur

approximately 2 hours after randomization. The additional time points for biomarker level determination will be

7.2.13.1. 1 hour (±15 min) post-drug initiation and SOC equivalent (3 hours post-randomization)

7.2.13.2. 3 hours (±15 min) post-drug initiation and SOC equivalent (5 hours post-randomization)

7.2.13.3. 24 hours (±30 min) post-drug initiation and SOC equivalent (26 hours post-randomization)

7.2.14. To investigate for possible rebound effect, final biomarker levels will also be obtained 24 (±8) hours post-drug discontinuation. Therefore 6 total sets of biomarker levels will be obtained in the angiotensin II arm compared to 5 in the SOC arm (as outlined in Table 2 – Biomarker Assay Schedule).

7.2.15. Exploratory analyses of the relationship between changes in biomarker levels and the other secondary endpoints will be performed.

7.2.16. Exploratory subgroup analyses aimed at identifying clinical syndromes (e.g., septic shock complicated by AKI or ARDS) 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 the biomarker (total renin, active renin, and DPP3) assays. The renin levels will be performed by the CTSC Translational Laboratory (T-laboratory). The DPP3 assays will be performed using a point-of-care (POC) analyzer housed in the Transfusion Medicine Service section of the Pathology Department near Dr. Nielsen's office on the second floor of UNMH.

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 in the DOIM and in the section of Transfusion Medicine Services in the Department of Pathology. He serves as an attending on the medical ICU and transfusion medicine (therapeutic pathology) services 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 in 2019, 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 at UNMH.*

9.3. 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.

9.4. 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.

9.5. The DOIM Clinical Trials Unit (CTU) will be used to provide research coordinator support for this study. The CTU is led by codirectors Dr. Lana Melendres-Groves and Dr. Gregory Mertz in the DOIM. The CTU has successfully provided coordinator support to three similar clinical trials, evaluating AKI and/or sepsis therapeutics, carried out by Drs. Nielsen and Teixeira over the last three years in the adult ICUs at UNMH. The primary coordinator for the trial is anticipated to be Natalie Weiss, RN, who has years of experience in coordinating clinical trials in the ICU and caring for critically ill patients as a bedside ICU RN at UNMH.

9.6. The CTSC T-Laboratory will be used to perform the total renin and active 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 or other CTSC T lab staff under her supervision.

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, angiotensin II will not be added as a clinically available order in this PowerChart order set. Instead, this titration scheme will be provided to the ICU RNs who care for patients assigned to the angiotensin II arm and all angiotensin II orders will placed via IDS.

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 restricted 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 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.

12.1.4. In the intervention arm, the second vasopressor added to norepinephrine will be open-label titratable angiotensin II

12.1.5. In the SOC arm, vasopressor(s) added to norepinephrine, if any, will be determined by the clinical team.

12.1.6. 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 Cerner PharmNet order template 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.

12.1.7. For research purposes, we will be collecting serial blood samples for dedicated renin and DPP3 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. We will ask the subjects to remain recumbent for at least 30 minutes prior to each renin assay. For DPP3 testing, 1-mL samples of whole blood will be collected and promptly analyzed used using a point-of-care analyzer.

12.1.8. 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 total renin, active renin, and DPP3 assays, no testing will be done as part of the research protocol.

12.1.9. The study will be conducted in 3 phases, a screening/enrollment phase (which ends at study drug initiation in the angiotensin II and at the equivalent time point in the SOC arm) and 2 study phases, a treatment phase (time 0 to 72h) and a follow-up phase (72h to hospital discharge).

12.2. Phase I (screening)

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 for 30 minutes 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 SOC. Study drug angiotensin II will be initiated once available at the bedside.

12.2.5. Random group allocation will be performed by UNMH IDS pharmacists and therefore will be completely separated from the investigators recruiting patients for the trial. IDS Pharmacy will design a

randomization table prior to study initiation. This will be accomplished with the Excel RAND() function and an appropriate block size to ensure equal but unpredictable group assignments. The randomization table will be stored securely in a location accessible only to IDS staff. In particular, the clinical investigators screening and recruiting for the study will not have access to the randomization table. Once an individual subject/LAR consents to the trial, the investigator will notify the IDS pharmacist who will access the randomization table and report the group assignment (angiotensin II or SOC) back to the investigator. Randomization will occur once a patient on a dose of ≥0.10 mcg/kg/min of norepinephrine monotherapy for at least 30 minutes provides consent. Randomization, for patients allocated to the angiotensin II (intervention) arm, will trigger preparation of study drug (angiotensin II) by the IDS pharmacist. IDS Pharmacy will also design and securely maintain data-collection forms over the life of the study, using the Vestigo® research-pharmacy system for recordkeeping and reporting.

12.2.6. At consent/randomization in both arms, blood will be collected for pre-baseline biomarker levels. Subsequently, at drug initiation (for the angiotensin II arm) and the equivalent time point in the SOC arm, blood will be collected for baseline biomarker 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 study drug in the angiotensin II and at the equivalent timepoint in the SOC arm.

12.3.2. 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 (attached), in concordance with the approved Nursing Department Titration Guideline (attached).

12.3.3. In the control group, vasopressor therapy will be titrated by the clinical team per usual SOC (as outlined in the Nursing Department Titration Guideline, attached).

12.3.4. In both the angiotensin II and SOC arms of the study, a MAP goal of ≥65 mmHg will be required during phase II. This MAP goal will be the only aspect of care that will be dictated by study protocol in the SOC arm.

12.3.5. In the angiotensin II arm, 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.

12.3.6. For research purposes, additional blood for repeat biomarker levels will be collected at specified intervals:

12.3.6.1. 1 hour (±15 min) post-drug initiation in the angiotensin II arm or the equivalent time point in the SOC arm

12.3.6.2. 3 hours (±15 min) post-drug initiation in the angiotensin II arm or the equivalent time point in the SOC arm

12.3.6.3. *24 (±30 min) hours post-drug initiation in the angiotensin II arm or the equivalent time point in the SOC arm*

12.3.7. If angiotensin II is discontinued before 48h, repeat biomarker levels will be collected during phase II at 24 (±8) hours post-drug discontinuation.

12.3.8. Apart from these total renin, active renin, and DPP3 assays, all data collected (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 (>100/min sustained for ≥1 hour), 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 angiotensin II will have angiotensin II weaned off, with norepinephrine increased as needed to achieve the angiotensin II wean. Subjects requiring >0.2 mcg/kg/min of norepinephrine in order to wean off angiotensin II will have an alternative SOC vasopressor agent, as selected by the treating ICU team, initiated. The ICU RN will have 1-2 hours (i.e., until hour 73-74) to complete the angiotensin II wean.

12.4.2. If angiotensin II is continued beyond 48h of therapy, the post-discontinuation biomarker levels, at 24 (±8) hours post-drug discontinuation, will fall during phase III.

12.4.3. All additional outcomes data will be obtained from the EMR as obtained per standard of care.

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

12.5. The drug being studied, angiotensin II, is FDA-approved for the indication (vasodilatory shock) under investigation.

12.6. Biomarker Testing:

12.6.1. Renin:

12.6.1.1. 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).

12.6.1.2. Two types of renin assay will be performed:

12.6.1.2.1. Total renin levels (including both active and non-active renin) will be measured using Human Renin Quantikine ELISA Kit (R&D Elisa - Cat # DREN00). This assay requires a 25-µL plasma sample.

12.6.1.2.2. Active renin levels will be measured using DRG International Inc. Renin (active) ELISA (Research Use Only, SKU EIA5125R). This assay requires a 50-µL plasma sample.

12.6.2. The procedure for blood collection for DPP3 level will be the same at all time points: 1 mL will be collected (from arterial catheter, from central venous catheter, or -- if necessary -- peripheral venipuncture) in a lavender top (EDTA) tube. The DPP3 analyzer (Sphingotest IB10 DPP3) and cartridges will be donated by 4TEEN4 Pharmaceuticals GmbH/SphingoTec GmbH to UNM and Dr. Nielsen to carry out this research. The DPP3 point-of-care (POC) assay can be run by the PIs or research coordinators on whole blood within 2 hours of sample collection without any additional processing, with results available within 25 minutes. The POC analyzer is small in size with limited footprint (2.4 kg; 17.5 x 33 x 18 cm).

12.6.3. The total renin, active renin, and DPP3 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 or DPP3 assays.

12.6.4. Though all other test results will be pragmatically obtained from the EMR as part of SOC, renin and DPP3 levels are not currently SOC tests for septic shock and therefore are experimental for this purpose.

12.6.5. Samples will be shipped to **ASKA Biotech GmbH** for further analysis of DPP3 samples that produce errors.

13. Data Analysis

13.1. As outlined above, the primary outcome will be the ability of the baseline biomarker levels obtained at drug initiation to predict response specifically to angiotensin II as defined by reduction in NED at 3 hours post-drug initiation. This outcome will be assessed via the following stepwise analysis, which will be reproduced 3 times, once each for total renin, active renin, and for DPP3.

13.1.1. First, the ability of our biomarkers (our **primary intermediary outcomes**) to predict NED at 3 hours (our **primary proximate outcome**) will be assessed by simple linear regression. Because the prior data suggest clear directionality to the relationship between renin and DDP3 levels and response to angiotensin II (i.e., that *higher* baseline biomarker levels are

likely to produce an enhanced response to angiotensin II), we will use a one-tailed sided alpha of 0.05.

13.1.2. To determine if the ability of baseline biomarker levels to predict response to vasopressor therapy is specific to angiotensin II or a general feature of septic shock treated with vasopressors, we will next perform another simple regression between the baseline biomarker level and vasopressor response in the SOC to first assess if there is any relationship between baseline biomarker levels and SOC vasopressor therapy.

13.1.3. We next perform a multivariable regression analysis of the entire cohort to evaluate the relationship between baseline biomarker level and total vasopressor dose in NED at 3 hours, using treatment arm (angiotensin II vs. SOC) as a co-variable. For this analysis, the NED for all vasopressors other than angiotensin II will be determined as per dose equivalency published by Jentzer et al. *Chest* 2018 Aug;154:416-426 (i.e., same equivalency used in ATHOS-3). To determine NED in the angiotensin II arm, the angiotensin II dose will be converted to NED using a factor of 0.0025 as proposed by Kotani et al. *Crit Care* 2023 Jan 20;27(1):29.

13.1.4. Given the possible confounding effect of severity of illness on the relationship between biomarker levels and angiotensin II response, we will repeat the multivariable regression analysis using baseline biomarker levels (**primary intermediary outcome**), treatment arm (angiotensin II vs. SOC), and SOFA score (**primary co-variable**) at baseline as predictor variables and total NED at 3 hours (**primary proximate outcome**) as the outcome variable.

13.2. As a secondary outcome, we will repeat the primary outcome analysis of the relationship between biomarker levels, treatment group, severity of illness, and NED at 3 hours using the *pre-baseline* biomarker level.

13.3. As a secondary outcome, we will repeat the primary outcome analysis of the relationship between biomarker levels, treatment group, severity of illness, and NED at 3 hours using *changes* in biomarker level (rather than baseline or pre-baseline biomarker levels).

13.4. Though we anticipate our trial will be too small to provide adequate power for these analyses, we will perform the additional exploratory analyses:

13.4.1. Analyses of the secondary endpoints and the safety endpoints by treatment group will be done using logistic regression and linear regression as appropriate for binary and continuous variables, respectively.

13.4.2. For secondary endpoints of particular interest (key secondary outcomes, namely hospital and ICU mortality and need for RRT or mechanical ventilation), multivariable analysis will be carried out to further explore the relationship between the treatment groups, biomarker levels, and illness severity (SOFA score) and outcomes.

13.4.3. Subgroup analyses of the primary proximal endpoint (NED at 3 hours) and the key secondary outcomes we be carried out in the prespecified subgroups of patients with AKI and patients with ARDS.

13.4.4. We will assess whether angiotensin II discontinuation is associated with an increase in total renin, active renin, or DPP3 levels at 24 hours post-discontinuation and whether this increase is associated with any of the key secondary outcomes.

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 an FDA-approved therapy to SOC, 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 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 an FDA approved treatment and SOC, 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 (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 clinical equipoise between angiotensin II and SOC has 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 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. Local electronic records will be stored on the "N:\ Research-Studies network drive.

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 SOC vs. use of an FDA approved medication being used for the labeled indication. 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 biomarker 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. The therapy (angiotensin II) being investigated in this trial is FDA-approved and labeled for the condition being treated (vasodilatory shock) and is considered standard of care. 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 vasodilatory 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 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. 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 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 English consent, and all other applicable documents, will be fully translated after English versions have been approved.

25.12.3. 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., Dr. J. Pedro Teixeira), 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.

25.12.4. 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 total renin, active renin, and DPP3 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. Angiotensin II is an FDA-approved drug 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. For this study, IDS will be responsible for the custody, accountability, and dispensation of angiotensin II throughout the trial according to IDS policies and practices.

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. Waiver of Documentation of Consent

N/A

39. Alteration of Consent

N/A

40. Full Waiver of Consent/Parental Permission

N/A

41. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

N/A

42. Full Waiver of HIPAA Authorization (Checklist)

N/A

43. Other Waiver Types (Checklist)

N/A

44. 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 SOC and an FDA-approved treatment 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, the treatment being studied, angiotensin II, is FDA-approved for septic shock and appears to be an effective and safe therapy. 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 drug being studied (angiotensin II) in this trial appears to be at least as beneficial and safe as the other vasopressor agents available as second-line therapy for septic shock (e.g., vasopressin, 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.

45. Medical Devices (Checklist)

N/A

46. Export Control (Checklist)

N/A

47. Data Transfer/Sharing/Storage (Checklist) (required –do not delete even if the answer is "No")

Data Use Agreement (DUA) Contacts:

Sponsored Projects Office

- HSC-PreAward@salud.unm.edu

Privacy Office

- HSC-Privacy@salud.unm.edu

Information Security Office

- HSC-ISO@salud.unm.edu

NOTE: For any data transfer/sharing questions or for help filling out this section, please email all contacts listed above.
All information stated in this section must be congruently stated in all other applicable sections of the protocol.

Provide all information requested, meaning all questions must be answered, if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will UNM data be transferred/shared with an external entity (i.e. another institution, company, etc.) or will an external entity's data be transferred/shared with UNM?

☒Yes. **If yes, all questions must be answered congruently based on protocol provisions.**

- If yes, does this research involve federal funding: ☐Yes ☒ No
  - If yes, provide the name of the funder:

☐ No. **If no, the remainder of this section does not apply.**

☐ The data is publicly available. **If the data is publicly available a data use agreement is not required and the remainder of this section does not apply.** "Publicly available" refers to data and/or biospecimens that are accessible to anyone in the general public, without the need for special qualifications, permissions, or privileges. Examples include data/biospecimens available for public purchase, searchable online, or available at a library.

Examples of types of identifiable data/biospecimens that are not considered publicly available are as follows:

Data in the electronic medical record;

Social media data labeled as "private" by the data owner, or not readily available without permission of the site Owner/Administrator under the Terms of Service of the site;

Data protected by Copyright; and

Data or biospecimens that have access restrictions (e.g. are only available to clinicians or qualififed researchers or may only be accessed on a secure server.

B. Indicate if the data is incoming and/or outgoing: **incoming**
C. Provide the name of the entity that data will be transferred/shared with: **4TEEN4 Pharmaceuticals GmbH**

D. Provide the name of the entity(s) that data will be transferred/shared with, if outgoing: N/A

E. Provide the external entity(s) contact name, email and phone number with whom the data agreement is going to be negotiated and executed with (i.e. Sponsored Projects Office contact or contracts department as applicable). List contact information for each external entity(s) that are involved with the project.

Contact Name	External Entity	Email	Phone Number
Dr. Karine Bourgeois. **Chief Scientific Officer**	**4TEEN4 Pharmaceuticals GmbH**	**bourgeois@4teen4.de**	**+49 3302 866 885-342.** **Cell Phone: +49 17624963381.**

F. Who is responsible for transmission of the data (include name, email address and phone number)? Dr. Karine Bourgeois
G. Who is responsible for receiving the data (include name, email address and phone number)? Dr. Joao Pedro Teixeira
H. Describe how the data will be securely transmitted/shared. If using an externally managed data transfer system, please include details about the system such as the URL for the site and information about who manages the security and maintenance. **Please note data cannot be transmitted/shared without assistance from UNM HSC Central IT**. ***Request UNM HSC Central IT transfer from the ISO office at HSC-ISO@salud.unm.edu. This means data cannot be transferred via email, cloud storage services such as Dropbox, OneDrive, and fax.***

☒ UNM HSC Secure File Transfer Protocol (SFTP)

☐ UNM HSC REDCap

☐ Other External Solution, and clarify:

I. For data being received/shared with non-HSC locations or entities, describe the following:

1. Where will data be stored and how will it be protected? UNM HSC requires data storage on the N:\Research -Studies network drive (i.e. encryption, password protection, access controls, use of REDCap, etc)?
   - **If** REDCap, who manages/owns REDCap (i.e. UNM HSC or other external entity)?
   - **If** REDCap or other external system is not UNM HSC REDCap managed/owned, please provide the name and contact information of owner and the access (login) link? N/A

     Provide IT security point of contact details for externally managed/owned REDCap: *N/A*

Redcap is not being used for incoming data.

2. What is the method being used for data collection and storage (i.e. electronic, hard copy, etc.)? electronic
3. How long will the data be stored? Must be congruent with section 16. indefinitely
4. Who will have access to data?
   Nathan Nielsen, MD
   Joao Teixeira, MD

J. Please list all specific data elements to be sent out (outgoing) and/or received (incoming) in the table below. If there are extensive data elements being shared, please summarize in the table below, and provide the document file name that contains the full list of data elements.

List Sponsor or Outside Entity	What is the classification of the data? Please indicate which of the following applies: De-identified Data; Limited Data Set; Protected Health Information See definitions after question "P".	List Incoming Data Elements	List Outgoing Data Elements
4TEEN4 Pharmaceuticals GmbH	**De-identified data**	**Subject ID DPP3 samples analysis results.**	**None**

K. 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? *The research does not require access, use, or disclosure of any of the 18*

individually identifiable protected health information identifiers. The data set is de-identified.

☐Yes (If yes, ensure section 9 ,Consent Process, completed)

☒No. If no, is HIPAA authorization altered or waived? If altered or waived, provide details:

L. Does the request to transfer/share data include clinical data that belongs to the UNM Health System? If data originates from the UNM Health System medical records, this question should be answered "Yes". ☒Yes ☐No

M. Is the external entity a "covered entity"? (HIPAA-covered entities include health care providers (i.e. hospitals, doctors, academic health centers), health plans, and clearinghouses.): ☒Yes ☐No

N. For outgoing data, is the data that is going to be transferred/shared owned or partially owned by another party? ☐Yes ☐No ☒NA, data is incoming only
If yes, please provide details:

O. Does the data have any restrictions other than HIPAA? ☐Yes ☒No
If yes, please provide details:

P. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health?
☐Yes ☒No
If yes, please provide details:

48. Specimen Transfer/Sharing (Checklist) (required –do not delete even if the answer is "No")

Please submit your material transfer agreement (MTA) request through Click ERA Agreements module so that Sponsored Projects Office (SPO) can begin working with you on the MTA. For any questions contact SPO via HSC-PreAward@salud.unm.edu.

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: *Outgoing*

C. Provide a description of the material/specimen that will be transferred/shared with the external entity: *DPP3 samples that produced errors (*N/A and/or >150 ng/mL)

D. Provide the name of the entity that specimens will be being transferred/shared with:

*DPP3 samples that produced errors (*N/A and/or >150 ng/mL) will be shipped to:

ASKA Biotech GmbH
Veltener Straße 12
16761 Hennigsdorf
Germany
Contact person: Susann Herrmann (mobile: +49 (0) 1516 7245797)

E. Provide the contact name, email and phone number with whom specimens are being transferred/shared with: **4TEEN4 Pharmaceuticals GmbH,**
Phone: +49 3302 866 885-342. Cell Phone: +49 17624963381.
bourgeois@4teen4.de
For clarity, the samples should be under Dr. Karine Bourgeois responsibility but the delivery will be done at ASKA Biotech GmbH. ASKA measures all our samples and produces our DPP3 kits and antibodies.

F. Who is responsible for sending out the specimens? Please note specimens cannot be sent out without a fully executed material transfer agreement. *Natalie Weiss, Nurse Study Coordinator.*

G. Who is responsible for receipt of the specimens? Please note specimens cannot be received without a fully executed material transfer agreement.
Dr. Karine Bourgeois
Chief Scientific Officer
bourgeois@4teen4.de

H. For specimens being transferred/shared with outside locations or entities, describe the following:
1. *Where is specimen storage and how will it be maintained in a secure manner? ASKA biotech. ASKA is ISO-certified, and all samples will be kept at -80 degrees in temperature monitored freezers.*
2. *What is method in which specimens will be collected and stored? The specimens will have previously been collected by venipuncture or via indwelling vascular catheters per the study protocol. All specimens will be stored in 80-degree freezers.*
3. *How long will the specimens be stored? The samples stored with ASKA Biotech for approximately 1 week. Once the samples are assayed, they will be destroyed with confirmation of such provided by ASKA to the UNM co-PIs.*
4. *Who will have access to the specimens? Only ASKA qualified personnel.*

The University of New Mexico Health Sciences Center

Consent and Authorization to Participate in a Research Study

Key Information for "DPP3, Angiotensin II, and Renin Kinetics in Sepsis (DARK-Sepsis) pilot: serum biomarkers to predict response to angiotensin II versus standard-of-care vasopressor therapy in the treatment of septic shock, a randomized controlled pilot trial" (HRRC ID 22-111)

You are being invited to take part in a research study about the use of medications to treat septic shock.

WHAT IS THE PURPOSE, PROCEDURES, AND DURATION OF THE STUDY?

By doing this study, we hope to learn more about how to best treat septic shock (very low blood pressure caused by a serious infection). Your participation in this research will last for the duration of your time in the hospital. The purpose of this investigation is to study whether two blood tests – renin and dipeptidyl peptidase 3 (DPP3) – can be used to guide how to treat the low blood pressure in septic shock and, in particular, if these blood tests can be helpful to decide if someone should be treated with a drug called angiotensin II. Angiotensin II appears to be an effective option to raise blood pressure in septic shock, but whether renin or DPP3 levels are useful to predict that angiotensin II is more effective than other medications is not clear. This study hopes to answer that question.

WHAT ARE THE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

Your participation will help us to learn how to best use this newer drug, angiotensin II, to treat septic shock and specifically how renin or DPP3 may be helpful in patients with septic shock treated with angiotensin II or other medications. This information will ultimately help us improve care of patients with septic shock. Currently, at the UNM Hospital, only patients who participate in this trial will have access to angiotensin II. For a complete description of benefits, refer to the Detailed Consent.

WHAT ARE THE KEY REASONS YOU MIGHT NOT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You may choose not to participate because there is a slight risk of breach of confidentiality (release of my personal information), because having blood drawn can cause discomfort, because answering questions may cause stress or emotional discomfort, or because you are participating in another trial. If you chose not to participate in this trial, we will treat your septic shock with other available drugs (e.g., norepinephrine, epinephrine, vasopressin, phenylephrine, or dopamine). For a complete description of the risks and of the alternate treatment/procedures, refer to the Detailed Consent.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits, or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The persons in charge of this study are Dr. J. Pedro Teixeira and Dr. Nathan Nielsen of the University of New Mexico Health Sciences Center, Department of Internal Medicine. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, please contact Dr. Teixeira; his contact information is 505-272-0407 or jteixeira@salud.unm.edu.

If you have any questions or concerns about your rights as a volunteer in this research, contact staff in the University of New Mexico Health Sciences Center (UNMHSC) Human Research Review Committee (HRRC) between the business hours of 8AM and 5PM, Mountain Standard Time (MST), Monday-Friday at 505-272-1129.

DETAILED CONSENT

Version 3 11Feb2025

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?

Individuals under the age of 18 and individuals who are not able to consent on their own and do not have an authorized person qualified to consent for them do not qualify for this study. Other medical conditions that would potentially exclude you include severe asthma or COPD; severe heart disease (new heart attack or shock from heart failure); severe disease of the aorta (aneurysm or dissection); new stroke; impairment of blood flow to the gut; active bleeding; untreated clots in leg veins or in the lungs (deep vein thrombosis, DVT, or pulmonary embolism, PE); severe liver disease; certain rare diseases (i.e., scleroderma or systemic sclerosis); certain conditions that result in compromised immune systems; allergies to angiotensin II or mannitol; pregnancy; or participation in another clinical trial.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The study will be conducted while you are hospitalized at University of New Mexico Hospital (UNMH). The research portion of this study will be conducted at UNM Health Science Center (UNM HSC). Your participation in the study will last the duration of your hospital admission.

The entire study will take place over 1 year. We anticipate including a total of 45-50 patients in the trial (20-25 in the treatment arm and 20-25 in the control arm).

WHAT WILL YOU BE ASKED TO DO?

By giving your consent, you allow us to do 3 things: (1) randomly assign you to one of two vasopressor treatments for septic shock, (2) collect your information, and (3) collect your blood for research.

The purpose of this investigation is to study whether two blood tests (renin and DPP3) can be used to guide how to treat the low blood pressure in septic shock. In particular, prior studies suggest that high blood levels of renin or DPP3 may be helpful to predict survival in septic shock and may specifically be useful in determining if the medication angiotensin II will be very helpful to increase blood pressure in septic shock. Angiotensin II is the synthetic form of a natural substance (a hormone) found in the body that increases blood pressure. Angiotensin II was approved to treat septic shock by the FDA in 2017. Angiotensin II appears to be an effective option to raise blood pressure in septic shock, but whether blood renin or DPP3 levels are useful to predict that angiotensin II is more effective than other medications is not clear. Because renin and DPP3 may be helpful to predict outcomes in patients with septic shock treated with medications other than angiotensin II, our study will have a control group in which renin and DPP3 levels are measured but angiotensin II is not used.

Vasopressors are medications used to increase blood pressure in patients with shock (severely low blood pressure). As part of standard of care, all patients in this trial will be treated first with norepinephrine for septic shock. Norepinephrine is the most commonly used vasopressor medication to treat septic shock and is considered the best first-line therapy for septic shock. Also, as part of standard of care, patients in this study will have a central venous catheter (a “central line”) and an arterial catheter (an “arterial line”) in place. A catheter is a small plastic tube inserted into a large vein or artery, similar to a regular “IV”, that allows us to give medications safely or to monitor your blood pressure in a continuous way. Central venous catheters are considered the safest way to administer vasopressors, particularly at higher doses. Similarly, arterial catheters allow for very precise (second-to-second) monitoring of blood pressure and are consider standard of care for moderate-to-severe septic shock. Patients will be included in this study if their blood pressure remains low despite norepinephrine. Angiotensin II,

the drug being studied, has been shown to be safe and effective at raising blood pressure when norepinephrine alone is not enough, but whether blood renin or DPP3 levels can reliably predict that angiotensin II will be effective is not clear. By giving us your consent, you allow us to randomly select either angiotensin II in addition to norepinephrine (in the treatment group) or other available vasopressors (in the control group) to treat septic shock.

By giving your consent, you also agree to allow us to collect information from you during the hospitalization and review or obtain medical records from this hospitalization so we can determine the duration, outcome, and severity of your illness; any underlying illness you have; and medications you have received.

Finally, by giving your consent, you allow us to draw blood to better study the effect of angiotensin II compared to standard of care. Specifically, preliminary studies suggest that two blood tests (renin and DPP3 levels) may help determine who benefits from treatment with angiotensin II. In this study, we are going to test if this is true by measuring renin and DPP3 levels in the blood of patients treated with angiotensin II. Other studies suggest that renin or DPP3 levels may be used do to predict survival in all patients with septic shock, including those not treated with angiotensin II. In our control group, we will measure renin and DPP3 levels in patients that are not treated with angiotensin II, which will help us tell if measuring renin and DPP3 levels gives us specific information about the usefulness of angiotensin II or if renin and DPP3 levels instead tell us if someone is likely to survive septic shock regardless of treatment. Because some studies suggest that changes in blood renin and DPP3 levels are more important than testing just one renin or DPP3 level, we will obtain renin and DPP3 levels multiple times in both arms of the study.

To measure these renin and DPP3 levels, we will need to collect an extra 3 milliliters (less than one teaspoon) of blood with each blood draw and will obtain blood up to 6 times over the first 4 days of the study. If you are assigned to the angiotensin II (treatment) arm, you will have up to 6 blood samples obtained; if you are assigned to the control (standard of care arm), you will have up to 5 blood samples obtained. Since we will only be enrolling patients in this study who have central venous catheters and arterial catheters in place, we can use these catheters to collect the blood. Collecting blood from catheters is a painless procedure but, in the rare instance that both of these catheters unexpectedly malfunction, we might have to collect blood by phlebotomy (placing a needle into a vein).

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

You will be included in the study only if your medical providers caring for you in the intensive care unit believe that you are a good candidate to be treated with angiotensin II. Angiotensin II is an FDA-approved treatment for septic shock. This approval is based on a trial which concluded that angiotensin II is likely to be a safe and effective treatment for septic shock.

However, the disease septic shock itself carries a significant risk itself of adverse events. In addition, though necessary to treat septic shock, all vasopressor medications carry risk of adverse events. Based on prior studies, these adverse events may include but are not limited to:

- New clot in artery or vein (arterial thrombosis or venous thromboembolism)
- New fast or abnormal heart rhythm (tachycardia or atrial fibrillation)
- Build-up of acid in the blood (lactic acidosis)
- Poor blood flow and injury to multiple organs, including:
    - The tips of your fingers or toes (peripheral limb or digit ischemia)
    - Gut (intestinal ischemia)
    - Heart (heart attack)
    - Brain (stroke)

  - Kidneys (kidney injury and failure)
- Low levels of blood platelets (thrombocytopenia)
- High blood sugar (hyperglycemia)
- New infection

These adverse events can occur with any patient with septic shock being treated with any vasopressor treatment, including patients who do not choose to participate in the study who are treated with the vasopressor treatments available outside of this study (such as norepinephrine, epinephrine, vasopressin, phenylephrine, or dopamine). Right now, it is not clear that any of these different treatments increase the risk of these adverse events more than the others.

Regardless of whether you choose to participate in this trial, your care in the ICU at UNM Hospital will be provided according to best practice guidelines to minimize these risks and to maximize the chance of a good outcome, but you are encouraged to ask your medical providers or the investigators about these risks of septic shock and its treatment.

If you are enrolled in this study, there is a slight possibility that you may experience a loss of confidentiality regarding your medical records. In order to protect the privacy of your clinical information, the research team will take measures like restricting access to your records and using security passwords and locked cabinets for storing the data. All data collected from this study will be retained and stored for a maximum of seven years after closure of the study.

As mentioned above, we will collect blood for this study. The amount of blood collected is small (a half-teaspoon or less at a time) and equal to or less than the amount blood that is normally taken daily from patients while hospitalized. Because we will require patients in this study to have a central venous catheter and an arterial catheter in place, we will plan to use these catheters to painlessly obtain the blood. However, in the rare instance that both catheters malfunction, we will obtain by blood by phlebotomy (needle placed into a vein). The drawing of blood with a needle from an arm vein usually causes mild pain (90%) and rarely causes a bruise (1%). There is a remote chance of fainting (less than 0.1%) and a very remote chance of infection (less than 0.01%).

There is always a chance that any medical treatment can harm you. The research treatments in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect.

If you choose not to participate in this trial, your condition will be treated with other medications (other vasopressors) available outside this study (potentially including norepinephrine, vasopressin, epinephrine, phenylephrine, or dopamine).

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

We do not know if you will get any benefit from participating in this study. As above, angiotensin II appears to be effective when used to increase blood pressure in septic shock. Though we need more data to be certain, earlier studies have suggested that angiotensin II might be especially effective for certain types of patients with septic shock (e.g., patients with high blood renin or DPP3 levels or patients with injured lungs or injured kidneys). Regardless, if you take part in this study, information learned may help others with your condition.

WHAT WILL IT COST YOU TO PARTICIPATE?

There are no additional costs associated with taking part in the study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave information or what the information is.

All information about your taking part in this study will be kept confidential. If you decide to participate, your records will be managed by the research team. If you participate, your medical records may be inspected by study personnel and the ethics committee at UNM. Any identifiable information, such as your name, will not be recorded on the study forms and will be replaced by a unique coded identifier to provide additional added confidentiality.

We will use a tool called REDCap to store data for this study. REDCap is a secure, web-based program to capture and store data at the University of New Mexico. Please be aware, while we make every effort to safeguard your data once received on servers via REDCap, given the nature of online servers, as with anything involving the internet, we can never fully guarantee the confidentiality of the data while still in route to the server.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study.

If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed, but no new data will be collected.

The investigators conducting the study may need to remove you from the study. The study medication will no longer be provided to you and will not be available for purchase. Though this is not anticipated, this could occur for a number of reasons. For example, we may need to remove you from the study if you develop or we discover a condition that would disqualify you from the study. If at any point the investigators believe that your participation in the study has more risk than benefit to you, you will be removed from the study.

Because all patients in this study will be in an intensive care unit at UNM Hospital and will already be on vasopressor treatment before starting the trial, all the patients will already be under close monitoring (with frequent or continuous measurements of vital signs such as blood pressure and heart rate, frequent assessment of symptoms by nurses, frequent adjustments of medications, and frequent laboratory testing). Because of this, no additional specific monitoring will be needed for this study on top of the close monitoring being provided as part of the standard of care in the intensive care unit, which will allow us to safely adjust the dose of the medications being used, angiotensin II in the treatment arm or other vasopressor(s) in the control arm. Though we do not expect this, we will also use all this information provided by this high level of monitoring to help us decide if we need to remove you from the study for safety reasons.

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEACH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may not take part in this study if you are currently involved in another research study that is evaluating another treatment or intervention, but participating in a separate non-interventional (i.e., observational) trial is allowed. It is important to let the investigator and your doctor know if you are in another research study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or you get sick because of something that is due to this study, you should call Dr. Teixeira at 505-272-0407 immediately.

It is important for you to understand that the UNM does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the UNM will not pay for any wages you may lose if you are harmed by this study.

Medical costs related to your care and treatment because of study-related harm will not be reimbursed by this study.

WILL I BE PAID FOR PARTICIPATING IN THIS STUDY?

You will not receive any financial rewards or payment for taking part in the study. Because this study is analyzing a treatment (angiotensin II) that is FDA-approved for the condition being studied (septic shock) and the ideas being tested (e.g., the idea that renin or DPP3 levels may be a good way to figure out if angiotensin II will be a helpful treatment) are based on prior scientifically sound research, the risk of participating in this study is reasonable despite the lack of payment.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

You will be informed if the investigators learn new information that could change your mind about staying in the study. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESARCH TESTS?

In this study, the bulk of the data collected will be the results of tests that are being done already for the purposes of your medical care. The blood collected will be used to measure the levels of substances called renin and DPP3, but these results will not be shared with you or your medical team. We are measuring renin and DPP3 levels because there is a theory that doing so can be helpful in treating septic shock, but this theory has not been proven and, for this reason, sharing the information with you or your medical team currently has no benefit.

FUTURE USE OF YOUR PROTECTED HEALTH INFORMATION

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, or date of birth.

HIPAA AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATIN (PHI).

As part of this study, we will be collecting health information about you and sharing it with others without identifying you. Links to your name and identifiable health information will be kept on a secure online database (REDCap) and will not be shared with others. This information is “protected” because it is identifiable or “linked” to you. Any information which does identify you is kept confidential and complies with the Health Insurance Portability and Accountability Act (HIPAA).

PROTECTED HEALTH INFORMATION (PHI)

By signing this Consent Document, as described in this consent form, you are allowing the investigators and other authorized personnel to use your protected health information for the purposes of this study. This information includes results of physical exams, medical history, and results of blood tests.

In addition to researchers and staff at UNM HSC and other groups listed in this form, there is a chance that your health information may be shared (re-disclosed) outside of the research study and no longer be protected by federal privacy laws. Examples of this include health oversight activities and public health measures, safety, monitors, other sites in the study, companies that sponsor this study, and government agencies such as Food and Drug Administration (FDA).

Right to Withdraw Your Authorization

Your authorization for the use and disclosure of your health information for this study shall not expire unless you cancel this authorization. This is because the information used and created during the study may be analyzed for many years and it is not possible to know when this will be complete. Your health information will be used or disclosed as long as it is needed for this study. However, you may withdraw your authorization at any time provided you notify the UNM investigators in writing. To do this, please send letter notifying them of your withdrawal to:

Dr. J. Pedro Teixeira
MSC10 5550
1 University of New Mexico
Albuquerque New Mexico 87131

While you are in the hospital, you may also withdraw by speaking with a member of the research team or by calling Dr. Teixeira at 505-272-0407. You may also be withdrawn from the study if the investigator feels it is in your best interest to withdraw you from the study.

Please be aware that the research team will not be required to destroy or retrieve any of your health information that has already been used or shared before the date that your withdrawal is received.

The researchers agree to only share your health information with the people listed in this document. Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of New Mexico;
- Current or future payments to the University of New Mexico;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to Dr. J. Pedro Teixeira, MSC10 5550, 1 University of New Mexico, Albuquerque, NM 87131-0001 to inform him of your decision.
- Researchers may use and release your health information already collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

The use and sharing of your information have no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of New Mexico Health Sciences Privacy Officer between the business hours of 8am and 5pm Mountain Pacific Time, Monday-Friday at (505) 272-1493.

WHAT IF YOU HAVE QUESTIONS LATER ON?

If you have questions related to this research, you can contact Dr. Teixeira at 505-272-0407. If you have questions, problems, or concerns about your participation in the research and would like to speak with someone other than the research team, you may call the UNM HSC Human Research Protections Office at (505) 272 1129. You may also call this number if you have questions about your rights as a research subject. For more information, you may also access the HRRC website at http://hsc.unm.edu/som/research/hrrc/ or http://hsc.unm.edu/research/hrpo/.

INFORMED CONSENT SIGNATURE PAGE (HRRC ID 22-111)

You are participating or are authorized to act on behalf of the participant. This consent includes the following:

- Key Information Page
- Detailed Consent

You will receive a copy of this consent form after it has been signed.

_____ _____

Signature of research subject **Date**

**research subject's legal representative may be allowed to provide consent by phone*

_____

Printed name of research subject

_____

**If applicable, printed name of research subject's legal representative*

_____ _____

Signature of legal representative, *if applicable* **Date**

*If applicable, please explain Representative's relationship to subject and include a description of representative's authority to act on behalf of subject:

_____ _____

Printed name of [authorized] person obtaining informed consent/HIPAA Authorization

Date

_____

Signature of [authorized] person obtaining informed consent/HIPAA Authorization