VASSPR Trial

Vasopressin for Septic Shock Pragmatic Trial

STUDY PROTOCOL

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1. ABBREVIATIONS AND DEFINITIONS

1.1 Abbreviations

AE	Adverse event
ED	Emergency Department
EMR	Electronic medical record
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ICU	Intensive care unit
ICD-9-CM	International Classification of Disease, version 9, clinical modification
ICD-10-CM	International Classification of Disease, version 10, clinical modification
DSMB	Data and Safety and Monitoring Board
ITT	Intention to treat
IV	Intravenous
MAP	Mean arterial pressure
PI	Principal investigator
PHI	Protected health information
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SOFA score	Sequential Organ Failure Assessment score
SpO2	Oxygen saturation via pulse oximetry
SUSAR	Serious and unanticipated suspected adverse reaction
UP	Unanticipated problem

1.2 Definitions

- **Adverse event (AE):** Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.
- **Adverse reaction:** An adverse reaction means any adverse event caused by a study intervention or procedure. An adverse reaction is a subset of all suspected adverse reactions where there is a reason to conclude that the study intervention caused the event.
- **Hypotension**: Systolic blood pressure <90 mmHg or mean arterial pressure (MAP) <65 mmHg or, where applicable, receipt of vasopressor medication.
- **Shock**: Hypotension treated with a continuous infusion of one or more vasopressors.
- **Protected health information (PHI):** identifiable health information that is used, maintained, stored, or transmitted by a HIPAA-covered entity.
- **Serious adverse event (SAE):** Adverse events that meet criteria for seriousness.
- **Sepsis**: Life-threatening organ dysfunction resulting from a dysregulated host response to infection.
- **Septic shock:** Sepsis associated with hypotension treated with a continuous infusion of one or more vasopressors. For purposes of this trial, septic shock will be identified using international consensus criteria receipt of a vasopressor infusion associated temporally with receipt of antimicrobial therapy or a positive test for an infection not amenable to antimicrobial therapy.
- **Suspected adverse reaction**: Any adverse event for which there is a reasonable possibility that the study intervention or procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction (21 CFR 312.32(a)).
- **Serious and unanticipated suspected adverse reaction:** Unanticipated adverse events that are also serious and are judged to be possibly, probably, or definitely related to study procedures.

2. PROTOCOL SUMMARY

Title Vasopressin in Septic Shock Pragmatic (VASSPR) Trial

Background Septic shock is a common trigger for intensive care unit admission associated with substantial morbidity and mortality. Therapy includes prompt initiation of appropriate antibiotics, rapid source control, and hemodynamic resuscitation with intravenous fluid and vasopressors. However, the threshold at which to start secondary vasopressor support for patients who receive escalating doses of first-line vasopressors remains unclear.

Primary objective To compare the effect of strategies for septic shock management employing lower versus higher thresholds for initiation of vasopressin infusion as a secondary vasopressor on 28-day mortality among patients with septic shock.

Primary hypothesis A management strategy incorporating a lower threshold rather than a higher threshold for adding vasopressin as a secondary vasopressor will improve 28-day all-cause mortality among patients with septic shock when compared to a higher threshold for adding vasopressin.

Study design Pragmatic multicenter open-label adaptive embedded cluster-randomized cluster-crossover comparative effectiveness trial

Study treatments
(1) Lower-threshold for vasopressin initiation strategy: If clinical team places a study-specific threshold-based vasopressin initiation order, instruction to initiate fixed-dose vasopressin infusion (1.8 units/hr) if combined norepinephrine-equivalent dose of other vasopressors reaches ≥0.1 mcg/kg/min.
(2) Higher-threshold for vasopressin initiation strategy: If clinical team places a study-specific threshold-based vasopressin initiation order, instruction to initiate fixed-dose vasopressin infusion (1.8 units/hr) if combined norepinephrine-equivalent dose of other vasopressors reaches ≥0.4 mcg/kg/min.

Randomization Cluster-randomized cluster-crossover trial in which each hospital will be randomly assigned during the initial study month to a treatment strategy with subsequent crossover of their treatment strategy monthly.

Inclusion criteria
1. Age ≥18 years
2. Admitted to a study hospital emergency department (ED) or inpatient care unit
3. Administration of vasopressor(s) for septic shock

Exclusion criteria	None
Primary outcome	28-day all-cause mortality
Key secondary outcome	Renal replacement therapy-free days to day 28
Exploratory clinical outcomes	In-hospital all-cause mortality 90-day all-cause mortality ICU-free days to day 28 Hospital-free days to day 28 Vasopressor-free days to day 28 New receipt of renal replacement therapy after enrollment
Exploratory safety outcomes	Clinical diagnosis of new-onset acute coronary syndrome Clinical diagnosis of new-onset mesenteric ischemia Clinical diagnosis of new-onset extremity, nose, or ear ischemia Clinical diagnosis of vasopressor extravasation Clinical diagnosis of clinically-significant arrhythmia Clinical diagnosis of cardiogenic shock Cardiac arrest New-onset severe hyponatremia (serum sodium <120 mEq/L) Maximum lactate through day 7 Serum troponin above upper limit of normal through day 7
Analysis	Multivariable regression including a fixed effect for treatment assignment, fixed effects adjusting for patient characteristics, and a random effect for study hospital.
Estimated study duration	16 months (up to 22 months)
Estimated patient sample size	2050 patients (maximum 7000)

3. STUDY BACKGROUND, SUMMARY, AIMS, HYPOTHESES

3.1 Critical illness due to septic shock

Sepsis is a deadly and common syndrome that results when a maladaptive immune response to infection results in organ failure.[1,2] Across the U.S., sepsis results in at least 1.3 million hospitalizations annually associated with 15-20% mortality and over $23 billion in costs for Medicare alone.[2-5] Survivors suffer substantial disability and frequent rehospitalization.[6,7] Septic shock — defined by receipt of vasopressor support to achieve adequate blood pressure and maintain end-organ perfusion[8] — is particularly deadly. The 17% of septic patients with septic shock suffer even worse outcomes than sepsis patients generally, with mortality above 40% in some studies.[2,4,9]

3.2 First-line therapy for septic shock

Good quality evidence supports use of a titrated continuous infusion of norepinephrine as the first-line vasopressor to support target mean arterial pressure (MAP) ≥65 mmHg for sepsis patients with hypotension unresponsive to fluid resuscitation.[10-14] However, concerns persist about toxicities associated with catecholamine therapy for septic shock, including potential modulation of the immune response.[15-17] Such concerns may be particularly relevant for patients with more severe shock, who receive more than low-dose norepinephrine (i.e., >0.1 mcg/kg/min[a]) to maintain target MAPs.

3.3 Second-line vasopressor options for septic shock

For patients in whom norepinephrine monotherapy proves insufficient to achieve MAP targets, U.S. clinicians may choose among five alternative intravenous (IV) agents targeting three different receptor classes:

- Other catecholamines, including dopamine, epinephrine, and phenylephrine;
- Angiotensin II;[19,20]
- Vasopressin (analogues including selepressin and terlipressin are not available with labelled indication for shock in the U.S. market as of May 2023).

International guidelines and the Intermountain Health sepsis care process model recommend vasopressin as the preferred second-line vasopressor in septic shock.[10]

3.4 Vasopressin physiology and potential mechanisms of benefit in septic shock

Vasopressin, an endogenous peptide hormone synthesized in the hypothalamus and secreted from the posterior pituitary, is involved in regulation of plasma osmolality and fluid balance via V_2 receptors. At higher doses, however, the hormone acts a potent vasoconstrictor via V_1 receptors.[21] After a rapid increase early in septic shock, however, vasopressin levels appear to be relatively low in patients with established septic shock compared to other forms of shock.[22] Many experts believe that this represents a vasopressin deficiency in septic shock and suggest that supplementation with exogenous vasopressin may improve outcomes by avoiding catecholamine-induced tachyarrhythmias, myocardial damage, lactic acidosis, immunosuppression, and the tachyphylaxis sometimes observed with high-dose catecholamines.[15,16,23-27]

3.5 Evidence for vasopressin therapy in septic shock

Most trials of vasopressin in septic shock have been underpowered[28-31] or tested vasopressin as a first-line vasopressor.[32,33] The best available evidence comes from the Vasopressin and Septic Shock Trial

[a] References to norepinephrine and norepinephrine-equivalent doses employ norepinephrine base units.[18]

(VASST), which randomized 778 patients with septic shock receiving at least 5 µg/min norepinephrine to initiation of vasopressin (up to 1.8 units/hr) or norepinephrine alone. Randomization was stratified by severity of shock with patients randomized in the less severe stratum if the patient's norepinephrine dose was 5 to 14 µg/min in the hour prior to randomization and the more severe stratum if the norepinephrine dose was 15 µg/min or higher. The trial did not show benefit from vasopressin overall (28-day mortality 39% vs 35%; p=0.26), but there was possible benefit from vasopressin among patients with less severe shock (28-day mortality 27% vs 36%, p=0.05). A formal analysis of effect modification by severity of shock did not achieve statistical significance (p=0.10), but that analysis was particularly underpowered.[34] Some have argued that these results suggest no benefit from vasopressin,[35-37] while others have suggested that vasopressin may have benefit if started earlier in the course of septic shock when norepinephrine doses are lower,[38,39] a hypothesis supported by a recent multihospital observational analysis.[40] No subsequent studies, however, have specifically evaluated the threshold for vasopressin initiation. Renal benefits from use of vasopressin in septic shock suggested by a *post hoc* analysis of the VASST trial[41] and small trials[30,42] have so far not been confirmed in larger trials, though importantly the key trial on this topic used vasopressin as a first-line agent rather than an adjunct to norepinephrine.[33] Overall, while data on vasopressin have led international guidelines to recommend addition of vasopressin infusion for patients "with inadequate MAP levels" on norepinephrine,[10] the guidelines do not indicate a specific threshold at which vasopressin should be started. Instead, they provide a broad "reasonable" range of doses at which vasopressin may be initiated.

3.6 Practice variation in vasopressin use

The lack of evidence to inform the dose of norepinephrine at which vasopressin should be initiated drives dramatic variability in the treatment of septic shock in routine clinical care.[43,44] Further, the lack of definitive evidence of clinical benefit from vasopressin plus rising cost (the price of vasopressin increased 50-fold in 2016) have led many hospitals to alter clinical protocols and restrict the drug's usage despite limited evidence regarding the effect of these changes.[45-48] In an analysis of over 500,000 patients admitted to 532 hospitals, the proportion of hospitals' septic shock patients receiving vasopressin varied from 0 to 70%, with hospital a more important predictor of vasopressin receipt than any patient characteristic except the presence of respiratory failure.[44] Another recent study of 252 U.S. hospitals similarly found 15-fold between-hospital variation in the average dose of norepinephrine at which vasopressin was started, ranging from <10 µg/min to nearly 90 µg/min (Figure 1).[43] Within Intermountain Health, we have observed similar variability in the dose of norepinephrine at which vasopressin is initiated. Among 422 patients with septic shock treated

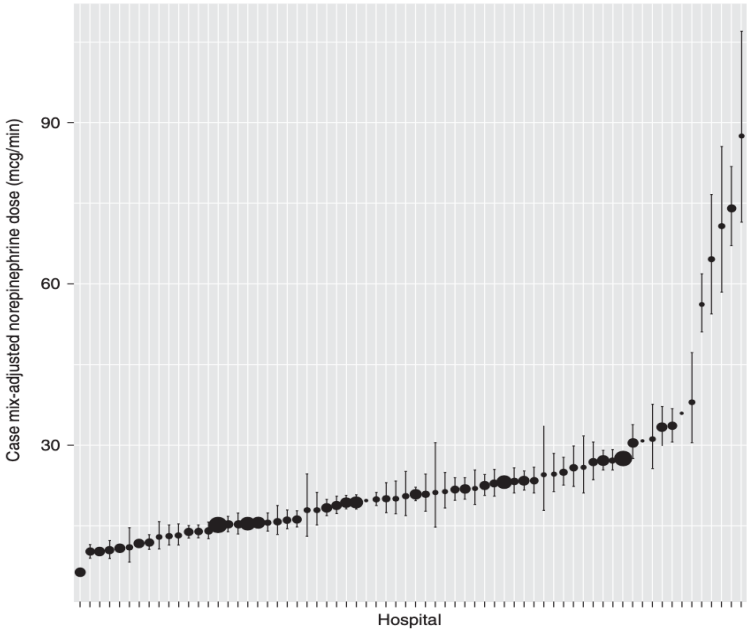

Figure 1. Practice variation for the initiation threshold for second-line vasopressor initiation among 69 U.S. hospitals after case mix adjustment (figure from Bosch *et al.* Annals Am Thorac Soc, 2021; 18: 2049-57).[43]

with vasopressin in 2021, the median norepinephrine dose at which vasopressin was initiated was 0.28 mcg/kg/min, but between-patient variability was significant: 5% of patients started on vasopressin when norepinephrine was ≤0.05 mcg/kg/min and 25% started at or below 0.17 mcg/kg/min of norepinephrine while an additional 25% of patients started vasopressin at or above a norepinephrine dose of 0.45 mcg/kg/min and 16% were not started on vasopressin until the norepinephrine dose was ≥0.60 mcg/kg/min (more than twice the median, Figure 2A). Patient characteristics (age, sex, comorbidity burden, and organ failure severity) were not associated with the norepinephrine dose at which vasopressin was initiated for a particular patient. This variability occurred both within and across the five hospitals within the system where ICU patients are managed by bedside intensivists. After accounting for differences in case mix, the use of vasopressin among patients with septic shock at referral hospitals ranged from 17% to 38% (p<0.001) and the median norepinephrine dose at which vasopressin was initiated ranged from 0.14 to 0.64 mcg/kg/min (p<0.001; Figure 2B). Taken together, these data demonstrate both substantial arbitrary (non-patient motivated) care variation and demonstrate substantial equipoise both nationally and within Intermountain Health with regard to the optimal threshold for vasopressin initiation.

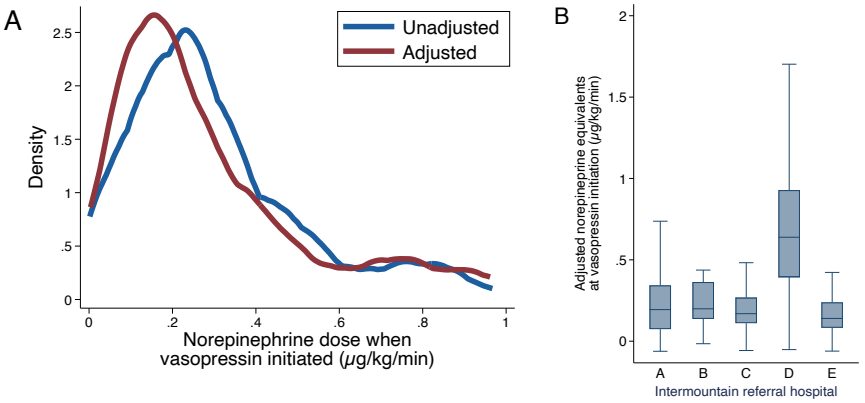

Figure 2. Practice variation at the (A) patient and (B) hospital level for vasopressin initiation threshold among 422 Intermountain Health patients treated with vasopressin for septic shock in 2021.

3.7 Primary objective

To compare the effect of strategies for septic shock management employing lower versus higher thresholds for initiation of vasopressin infusion as a secondary vasopressor on 28-day all-cause mortality among patients with septic shock.

3.8 Primary hypothesis

A management strategy incorporating a lower threshold for adding vasopressin as a secondary vasopressor will improve 28-day all-cause mortality among patients with septic shock when compared to a higher threshold for adding vasopressin.

3.9 Study overview

To compare the effectiveness of alternative strategies currently within the spectrum of usual care for refractory septic shock management, we will conduct a multicenter, open-label, adaptive, cluster-randomized cluster-crossover embedded pragmatic clinical trial (Figure 3). Patients with septic shock in one of Intermountain Health's 13 hospitals in Utah and Idaho with intensive care units (ICUs) during a 2-year period will be included in an analysis comparing clinical and safety outcomes resulting from hospital-level implementation of treatment strategies recommending initiating fixed-dose vasopressin when first-line vasopressors reach a norepinephrine-equivalent infusion rate of 0.1 versus 0.4 µg/kg/min.

4. STUDY POPULATION AND ENROLLMENT

4.1 Setting

Intermountain Health is a nonprofit health system based in Salt Lake City, Utah, with 24 hospitals in Utah and Idaho and 8 additional hospitals in Colorado and Montana. The proposed trial will take place at Intermountain Health's 13 adult hospitals with ICUs in Utah and Idaho. Study hospitals range in size from 25-472 beds and include 1 tertiary teaching hospital, 3 regional referral hospitals, and 9 community hospitals. (Table 1). Study hospitals employ the bitartrate formulation of norepinephrine.[18] Product labeling, clinical administration and documentation of norepinephrine doses use norepinephrine base units. Subsequent references to norepinephrine doses employ norepinephrine base units.

Table 1. Intermountain Health study hospitals.

Hospital	Location	Description	Hospital beds	2021 sepsis cases
Intermountain Medical Center	Murray, UT	Tertiary/teaching	472	2207
St. George Regional Hospital	St. George, UT	Regional referral	245	1819
Utah Valley Hospital	Provo, UT	Regional referral	395	1283
McKay-Dee Hospital	Ogden, UT	Regional referral	321	1405
LDS Hospital	Salt Lake City, UT	Community	250	382
Logan Regional Hospital	Logan, UT	Community	146	578
Riverton Hospital	Riverton, UT	Community	97	406
Alta View Hospital	Sandy, UT	Community	71	291
American Fork Hospital	American Fork, UT	Community	89	673
Cedar City Hospital	Cedar City, UT	Community	48	283
Park City Hospital	Park City, UT	Community	37	173
Cassia Regional Hospital	Burley, ID	Community	25	174
Layton Hospital	Layton, UT	Community	50	328

4.2 Study population

The proposed trial will enroll adult patients (age ≥18 years) admitted to a study hospital with septic shock.[1,2,49]

4.2.1 Inclusion criteria

1. Age ≥18 years
2. Admitted to a study hospital emergency department (ED) or inpatient care unit
3. Administration of vasopressor(s) for septic shock*

   * Determined by concurrent (1) active vasopressor infusion and (2) an active vasopressor administration order incorporating an indication for septic shock. The indication for vasopressor administration is documented by the ordering provider in real time within the computerized order for vasopressor administration. See Appendix A for applicable vasopressors.

4.2.2 Exclusion criteria

There are no exclusion criteria.

4.2.3 Inclusion/exclusion criteria rationale

This study will address vasopressor management of septic shock in adults. The trial will include patients administered vasopressors for whom clinicians indicate a suspected or confirmed diagnosis of septic shock. Children <18 years of age will be excluded because the mechanisms, manifestations, and management of infection and sepsis in children <18 years of age are distinct from those applicable to

adults and vary based on age group between birth and age 18 years. Moreover, septic shock care for children <18 years is performed by distinct care teams in distinct venues using distinct clinical care pathways.

4.3 Enrollment

Patients will be considered enrolled at the time that (1) patient is admitted to a study hospital ED or inpatient care unit; (2) clinician has entered an active order for vasopressors with an indication for suspected or confirmed septic shock; and (3) vasopressors are being infused. Day of enrollment is considered study day 0.

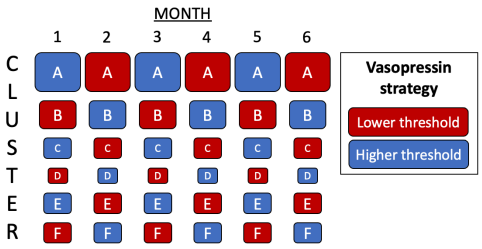

Figure 3. Simplified cluster crossover trial schematic including 6 variably-sized clusters in 6 monthly crossovers. *The actual trial will have 13 clusters and last 24-28 months. See Appendix B for full trial timeline/randomization schematic and study randomization assignments.*

4.4 Randomization

For this cluster-randomized cluster-crossover trial (Figure 3), study hospitals' initial assignment to lower or higher threshold strategy for vasopressin initiation will be determined by block randomization using a computer-generated random number sequence stratified based on four levels of historic hospital septic shock patient volumes. (For one stratum comprised of three hospitals, whether one or two hospitals are initially assigned the low threshold strategy will also be assigned randomly.) Thereafter, hospitals will crossover their treatment strategy monthly through the end of the study (see Appendix B and Sections 4.5 and 5.3).

4.5 Study duration

After a 4-month vanguard phase at one referral hospital (see Section 5.3), active study intervention and enrollment will begin at all study hospitals. The study will continue for approximately 16 months (maximum 22 months) at the vanguard hospital and 6-12 months (maximum 18 months) at each of the other 12 study hospitals. The date on which study hospitals cease study enrollment will be determined by each study hospital's transition from its current electronic medical record (EMR) system to a new EMR.[50-52] (Study hospitals are expected to transition EMRs in late 2025, with some study hospitals acting as pilot sites and transitioning EMRs in spring or summer of 2025. Definite information on each study hospital's EMR transition date is not expected to be available at the time the present trial begins enrollment.) Each study hospital will cease study interventions and patient enrollment preceding that hospital's EMR transition. The hospital's study closure date will be selected such that the amount of time that the hospital is actively enrolling is balanced across the two study arms (i.e., hospitals will have approximately equal time assigned to each vasopressin initiation strategy).

4.6 Treatment assignment

Patients' treatment assignment will be the strategy in place at the time and study hospital they meet all study entry criteria as described in Section 4.3.

4.7 Study population representativeness

Women and individuals of minoritized race and/or ethnicity will be enrolled in proportion to their representation in the population base served by study hospitals, specifically patients presenting to Intermountain Health hospitals located in Utah and Idaho. In order to provide generalizable data, there will be no specific selection criteria that differ between sex/gender and racial/ethnic groups. Hospitals in this study serve a combined population of over 2.9 million individuals, including 24% who are Latino or

Hispanic or of race other than white. We expect the sex, ethnic, and racial mix of the enrolled patients to reflect the population served.

4.8 Vulnerable subjects

The goal of this comparative effectiveness trial is to enroll a cohort that reflects the diversity of the U.S. sepsis population. We therefore anticipate that potentially vulnerable subjects will be eligible for the study, proportional to their membership in the overall population of septic shock patients who will ultimately benefit from the knowledge gained. Specific potentially vulnerable patient subjects include pregnant women, prisoners, and/or individuals with decisional impairment. Importantly, potentially vulnerable participants will not be singled out for inclusion, nor will they disproportionately bear the burden of research unlikely to benefit people like them in the future. Therefore, we believe these individuals should not be excluded from the study since the study is of no more than minimal risk, and in fact, attempting to exclude such individuals from cluster-randomized strategy interventions could increase clinical and privacy risks:

1. In many embedded cluster-randomized effectiveness trials generally and this trial specifically, it is not possible to prevent vulnerable subjects from receiving the study intervention (see Section 5.2) because it is fully integrated with usual care.[53-55] Clinicians will be empowered to tailor usual care to the individual need for each patient with septic shock.
2. The study aims to compare the effects of adopting two different, more specific guidelines for secondary vasopressor initiation in septic shock. Assessment for vulnerability status prior to study entry would preclude achievement of this goal because it would preclude delivery of the intervention via the implementation strategies applied in real-world practice to standardize clinical care based on guidelines.
3. Data on prisoner or incarceration status will not be explicitly collected.
4. Altered mental status is a very common manifestation or complication of sepsis. Excluding patients with decisional impairment would therefore severely bias results of the planned analyses and ultimately preclude obtaining an answer to the study's motivating question.

5. STUDY PROCEDURES

5.1 Study interventions

We will compare two usual care vasopressor management strategies: a lower versus a higher threshold for adding fixed dose vasopressin in septic shock. The two treatment strategies were selected to represent treatment strategies within the range of current usual practice both within the study health system and within the U.S. generally.

5.1.1 Lower-threshold vasopressin strategy

The lower-threshold strategy will target initiation of IV vasopressin at a continuous rate (1.8 units/hr) when the combined dose of other continuously-infused vasopressor medications reaches an equivalent of norepinephrine 0.1 mcg/kg/min.

5.1.2 Higher-threshold vasopressin strategy

The higher-threshold strategy will target initiation of IV vasopressin at a continuous rate (1.8 units/hr) when the combined dose of other continuously-infused vasopressor medications reaches an equivalent of norepinephrine 0.4 mcg/kg/min.

5.1.3 Rationale for selection of vasopressin initiation threshold strategies

The vasopressin initiation thresholds were selected as representative of treatment strategies used in routine clinical care as shown by internal data from the study health system, published data from a nationally-representative group of ICUs, consultation with sepsis experts, and input from patient representative and clinician stakeholders from the study health system's ICUs and EDs. Evidence considered included:

(1) The VASST trial[34] — the largest trial of vasopressin as a second-line vasopressor to date — suggested the possibility of improved outcomes among patients randomized to vasopressin who started on study drug while norepinephrine was <15 mcg/min (0.19 mcg/kg/min in an 80 kg individual), but lacked adequate statistical power to robustly evaluate the question of whether benefit might vary by infusion rate of norepinephrine at the time of vasopressin initiation.

(2) Observational data on current practice in the United States in a geographically-diverse dataset including 69 hospitals demonstrated that risk-adjusted hospital-level initiation thresholds for second-line vasopressors vary by over 10-fold.[43] Roughly 25-30% of hospitals in this study started second-line vasopressors in the vicinity of the lower threshold planned for the present study (norepinephrine 0.1 mcg/kg/min) for an average patient, while approximately 20% of hospitals started second-line vasopressors in the vicinity of the higher threshold planned for the present study (norepinephrine 0.4 mcg/kg/min) for an average patient.

(3) Nationally, some health systems — including Vanderbilt University Medical Center and the 40-hospital University of Pittsburgh system — restrict vasopressin initiation until other vasopressors reach a norepinephrine equivalent in the range of 0.5 mcg/kg/min.

(4) Within the study health system, norepinephrine equivalent vasopressor doses of 0.1 mcg/kg/min and 0.4 mcg/kg/min represented the 17th and 71st percentiles for patient-level vasopressin initiation thresholds, respectively. After accounting for patient characteristics, the selected thresholds represented the 24th and 76th percentiles, respectively (Figure 2A). At the hospital level, median norepinephrine dose at which vasopressin was started ranged from 0.14 to 0.64 mcg/kg/min even after case mix adjustment (Figure 2B).

5.2 Pragmatic implementation of study interventions

Strategy implementation will be embedded in routine care, applying pragmatic methods akin to those applied for evidence-based care protocols, thus encouraging adherence to the assigned strategy as best practice while allowing tailoring of care for individual patients based on clinicians' judgement.

5.2.1 Study-specific threshold-based vasopressin order

A new, study-specific order will be created in the study health system EMR's provider order entry module for threshold-based initiation of fixed-dose IV vasopressin infusion (1.8 units/hour [0.03 units/min]). The order's title will be "Threshold-Based Vasopressin for Septic Shock" or similar, explicitly indicating its intended use is restricted to patients with suspected or confirmed septic shock. Upon this order's entry by the treating clinical team, fixed-dose IV vasopressin infusion will become active medication for the patient, with automatic incorporation of medication administration instructions directing the clinical pharmacy and bedside nurse to initiate the vasopressin infusion when the total dose of first-line vasopressor(s) reaches 0.1 mcg/kg/min (lower threshold) or 0.4 mcg/kg/min (higher threshold) norepinephrine equivalents depending on study treatment assignment currently in place at the hospital where the patient is receiving care.

5.2.2 Methods for ordering the study-specific threshold-based vasopressin order

Clinical teams will be able to place a study-specific threshold-based vasopressin order via multiple pathways, including pathways designed to ease utilization of this order while also ensuring clinical teams are empowered to customize care for individual patients based on clinical judgement. As described in Section 5.2.1, once the study-specific order is placed, the threshold for vasopressin initiation automatically inserted in the order generated will alternate monthly per hospitals' randomized strategy assignment.

5.2.2.1 Direct study-specific threshold-based vasopressin order entry

Licensed clinicians, including attending and resident physicians and advanced practice clinicians will be able to access and order the study-specific threshold-based vasopressin order directly via the provider order entry search function. For key clinician types (e.g., emergency medicine and ICU physicians), the study-specific vasopressin order will be added to their "quick orders" interface. Pharmacists and nurses acting on behalf of a licensed independent physician will also be able to directly access and place the study-specific vasopressin order via their usual methods for entering a "verbal order."

5.2.2.2 Order sets for vasopressor management in septic shock

All existing vasopressor management order sets in the study EMR will be modified to include the study-specific threshold-based vasopressin order described in Section 5.2.1. In order sets specific to sepsis and septic shock, the study-specific vasopressin order will be pre-selected alongside norepinephrine. If clinicians use the septic shock order sets but believe an alternative approach to vasopressin administration is preferred for an individual patient, they may choose to order vasopressors (including vasopressin) outside of the septic shock order set or to modify default orders within the order set, including deactivating the preselected vasopressin or adjusting the ordered vasopressin dose.

5.2.2.3 EMR-embedded decision support

Clinical decision support embedded within the EMR will be deployed to remind clinicians caring for potentially eligible adult patients at a study ED or inpatient unit of the option to enter the order for

threshold-based vasopressin initiation described in Section 5.2.1. The decision support "pop up" alert will appear if (1) clinicians (including pharmacists and nurses acting on behalf of a licensed independent physician) are entering an order for vasopressors; (2) vasopressor orders' designated indication is infection potentially contributing to hypotension; and (3) a vasopressin order is not already present. The alert will incorporate:

1) A reminder that guidelines recommend adding vasopressin in septic shock with an inadequate mean arterial pressure on first-line vasopressors.
2) Two response options:
    a. An option to add the study-specific threshold-based vasopressin order;
    b. An option to continue with the original order without adding the study-specific threshold-based vasopressin order.

The alert will not appear if the patient has evidence in the EMR of a condition (e.g., existing diagnosis of digital ischemia) that could potentially alter the risk/benefit ratio for vasopressin utilization or for a lower or higher vasopressin initiation threshold (see Appendix C). The alert will also be silenced for clinician roles or situations for whom the alert is generally not applicable (e.g., cardiac surgeon).

5.2.4 Treatment delivery based on the study-specific threshold-based vasopressin order

Once a study-specific threshold-based vasopressin order is entered by the clinical team, usual care processes will be used for drug preparation by the clinical pharmacy and administration by the bedside nurse, with the exception that the vasopressin infusion is intended to be initiated only once the patient's other vasopressors reach the ordered threshold.

5.2.4.1 EMR-embedded vasopressin threshold notification for nurses

For patients with an active threshold-based vasopressin order, nurses will receive a notification from the EMR prompting vasopressin initiation when the patient's dose of other vasopressor reaches the assigned/ordered threshold based on real-time entry of vasopressor dose data into the electronic medical record.

5.2.4.2 Other support for threshold-based vasopressin initiation

Implementation strategies customized to the care setting and clinician roles will be utilized to support nursing and pharmacy adherence to the ordered vasopressin initiation threshold. Examples of potential implementation support strategies include:

- Discussion of their hospitals' current assigned threshold for vasopressin initiation during change-of-shift nurse huddles;
- Just-in-time education from ED pharmacists to ED nurses or from ICU telemedicine nurses/pharmacists to bedside ICU nurses triggered by ordering of the threshold-based vasopressin initiation order.

5.2.5 Utilization review and feedback

We will perform selective real-time monitoring of utilization of threshold-based vasopressin orders to allow ongoing support for appropriate utilization and education for clinical care teams.

5.2.6 Education and implementation support for clinical teams

Prior to study launch and periodically throughout the study, we will provide and/or make available education about the trial to clinical personnel — including physicians, advanced practice clinicians,

nurses, and pharmacists — who care for patients with septic shock. This education will be tailored for specific venues and audiences and may include information about current guidelines and data on use of vasopressin in septic shock, conditions and situations that may alter that risk/benefit of vasopressin use, practical guidance about ordering and executing threshold-based vasopressin orders, and education about notifying the study team about adverse events that are possibly related to study procedures. Procedures for ongoing measures to support awareness for physicians, advanced practice clinicians, nurses, pharmacists, and other relevant bedside personnel about the availability and successful utilization of the threshold-based vasopressin orders will be developed and customized as needed to the needs of individual hospitals and care units. Examples of potential strategies include those described in Section 5.2.4.2 as well as:

- Periodic discussion of the trial and utilization rates for the study-specific threshold-based vasopressin initiation order at clinical staff meetings, departmental grand rounds, and other similar venues.
- Just-in-time education from ICU telemedicine clinicians to bedside clinicians regarding the threshold-based vasopressin initiation order when a potentially suitable patient is identified.

5.2.7 Treatment exposure considerations

As described in Sections 4.3 and 4.5, in this pragmatic trial comparing two default strategies for septic shock management, patients' exposure to the assigned treatment strategy begins at study entry and treatment assignment for intention-to-treat analyses will be based on the date and time they meet all inclusion criteria at a study hospital. Patients may not receive vasopressin at the threshold dictated by their assigned treatment strategy for several reasons, including:

- The patients' clinical team does not order vasopressin;
- Vasopressin is initiated by the clinical team at a threshold other than the assigned via an order other than the study-specific threshold-based vasopressin initiation order.
- The clinical team enters the study-specific threshold-based vasopressin initiation order but patient's other vasopressors do not reach the assigned vasopressin initiation threshold.

Once a study-specific threshold-based vasopressin order is entered, the threshold for vasopressin for an individual patient will remain stable as long as that patient remains admitted to the study hospital and the order is not discontinued, even if the study hospital treatment assignment crosses over before patient completes treatment for septic shock. However, some patients assigned to one vasopressin management strategy for analyses may still receive treatment that partially or completely adheres to the alternative vasopressin management strategy in some situations. Examples include:

- Patients who are weaned off vasopressors after initially qualifying for trial inclusion but subsequently have vasopressors reordered after the study site has crossed over to the alternative vasopressin strategy;
- Patients who qualify for trial inclusion while study hospital is assigned to one vasopressin strategy but have a new threshold-based vasopressor order entered after the study site has crossed over to the alternative vasopressin strategy without weaning off vasopressors in the interim;
- Patients transferred between study hospitals randomized to different vasopressin strategies;
- Patients who qualify for trial inclusion, survive the hospitalization, and then have a subsequent readmission to a study hospital involving vasopressor administration for septic shock before the end of study follow up.

Patients will be analyzed in the group to which they were assigned at the time of initial enrollment, regardless of which treatments are subsequently received.

5.3 Vanguard implementation

At a single referral hospital (Intermountain Medical Center), the trial will launch 4 months before system-wide implementation (see Appendix B). During this vanguard phase, study personnel will optimize EMR and other procedures for supporting intervention implementation and adherence, data collection, and safety monitoring. Patients enrolled during the vanguard phase will be included in the intention-to-treat analysis.

5.4 Standard care

Irrespective of study or clinician-assigned vasopressin initiation strategy, all sepsis patients will receive then-current evidence-based care for sepsis as directed and administered by their clinical team. Sepsis care at study hospitals— including antibiotics, procedural source control (where applicable), fluid resuscitation, adjunctive steroid treatment, blood and body fluid cultures, and other aspects of supportive care — is guided by clinician judgment within the context of system-wide protocols and care monitoring for sepsis.[56] Vasopressor and vasopressin weaning will be at the discretion of patients' clinical care team. Key components of supportive care potentially modified by the tested vasopressor management strategies, including fluid resuscitation and adjunctive steroid treatment specifically, will be chosen by the clinical team and included as monitored care processes in study analyses.

5.5 Blinding

Due to the pragmatic design of the trial, blinding of patients, clinicians, and study personnel to treatment assignment is not practicable. Primary data collection for study outcomes, including the primary 28-day mortality outcome, will be obtained via data queries agnostic to treatment assignment, with any manual adjudication of endpoints and other study data also blinded to treatment assignment. A statistician blinded to treatment assignment throughout the trial will conduct final analyses.

6. DATA COLLECTION

Core analyses will employ data collected during routine clinical care and hospital operations. There will be no direct patient contact for collection of identifiable data or specimens.

6.1 Data collection

The Intermountain Health Enterprise Data Warehouse (EDW) is a centrally-managed, well-curated, and accessible database linking system-wide clinical, billing, laboratory, and other data.[57] Trial data managers will identify eligible patient subjects using EDW data and will generate a dataset specific to the proposed study by linking EDW data to additional data abstracted from the electronic health record. We will employ a preexisting linkage to Utah State death records and the U.S. Social Security Death Index for mortality ascertainment. Manual chart review will be employed as needed to validate and supplement electronically-available data and will use the Research Electronic Data Capture (REDCap) platform.[32]

6.2 Protected Health Information

Protected health information (PHI) including subject encounter codes, medical record numbers, birthdates, encounter event date and times, address, and social security number will be collected to allow manual chart abstraction, intervention implementation, manual review of electronic record for data completion and verification, and estimation of patient socioeconomic status and also to ensure accurate capture of mortality outcomes. Specific PHI data elements planned for collection are:

- Patient medical record number(s)
- Patient encounter ID code(s)
- Hospital/facility
- Date of birth
- Name
- Date/time of events related to hospitalization (e.g. outside hospital arrival/departure, ED arrival & departure, hospital admission & discharge), treatments, clinical testing and documentation, and other clinical events
- Date/time of death (if applicable)
- Address/zip code (for determination of residence at a nursing facility or other long-term care facility and estimation of socioeconomic status)
- Age (including age >89 years)

6.3 Variables/data elements

- Demographics
  - Age
  - Sex
  - Race
  - Ethnicity
  - Marital status
  - Preferred language
  - Residence prior to hospital admission (e.g. home, skilled nursing facility, long-term acute care hospital)
  - Insurance status/type

- Characteristics of index hospitalization
    - Type of admission to study hospital (e.g., emergent vs elective)
    - Source of admission to study hospital (e.g., ED of study hospital, ED of other Intermountain Health hospital)
    - Patient transferred from initial study hospital to another acute care hospital (yes/Intermountain Health, yes/other hospital, no)
    - Care location(s)
- Clinical data related to index hospitalization (with associated date/times as applicable)
    - Admission diagnosis
    - Illness severity scores (e.g. APS, APACHE IV score)
    - Comorbidities and comorbidity scores (e.g. Charlson index, Elixhauser index)
    - Chronic dialysis
    - Home medications
    - Acute SOFA score and components
    - Baseline SOFA score and components (up to preceding 10 years)
    - Baseline laboratory data (up to preceding 10 years)
    - Clinical care notes and authors
    - Index hospitalization diagnoses
    - Presence/source of infection diagnosed at key time points (e.g., ED arrival, antibiotic initiation, at time of vasopressor initiation)
    - Presence/source of infection on final assessment
- Clinical assessments (e.g. physical exam, vital signs, triage scores, RASS), laboratory, microbiology, diagnostic, and radiology testing related to index hospitalization
    - Assessment/test type/characteristics
    - Associated date/times
    - Test results
- Antibiotics, vasopressors, IV fluid, and other pharmacologic therapies
    - Pharmacologic agent
    - Route
    - Rate (if applicable)
    - Dose
    - Date/time(s)
    - Caregivers involved in therapy ordering and administration
    - Complications (if applicable)
    - Antibiotic spectrum scores
    - Costs of drug and administration
- Other clinical treatments and interventions (e.g. mechanical ventilation, central line placement, renal replacement therapy)
    - Treatment/intervention performed and characteristics thereof
    - Associated date/times
    - Complications (if applicable)
- Admission to hospital via ED (yes/no)
    - Mode of arrival to ED
    - ED disposition
    - ED length of stay
- Hospitalization outcomes
    - Hospital disposition

- In-hospital all-cause mortality
- Long-term all-cause mortality (e.g. 28-day, 90-day and 1-year mortality)
- Death date
- Healthcare charges, revenue, costs etc.
- Discharge diagnosis and procedure codes
- Diagnosis-related group
- Hospital length of stay
- ICU length of stay
- Post-discharge healthcare utilization (with dates/times and associated diagnoses)

6.4 Data management

Data analysts and research coordinators will collect data and record it in a custom-designed computer database. Data abstraction from electronic medical records will employ either standardized paper case report forms or a custom-designed interface maintained within Intermountain Health's secure Research Electronic Data Capture (REDCap) platform.[32] Outside REDCap, all electronic study data will be kept in a protected database on a protected computer and all paper forms will be kept in secured file storage. Each subject will be assigned a study identification number, and we will maintain minimal patient identifiers. Shared or presented data will be in anonymized or aggregate format such that individual patient subjects cannot be reidentified. An unblinded statistician will collate, analyze, and present relevant study data and other trial issues to the Data and Safety Monitoring Board (DSMB). A statistician blinded to both treatment assignment and data related to monitored care processes (see Section 7.2.4) will perform analyses of primary, secondary, and exploratory outcomes.

7. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

7.1 Primary exposure

The primary exposure will be the assigned vasopressin treatment strategy. For the primary intention-to-treat (ITT) analysis, study subjects will be treated as having received the treatment strategy in place at the time and hospital they first met all study inclusion criteria.

7.2 Outcomes

The day of study enrollment is considered study day 0. All outcomes are evaluated at the patient level. All-cause mortality outcomes are measured through day 90. All-cause 28-day mortality follow-up is incorporated into measurement of event- or treatment-free days. Other outcomes are censored at hospital discharge unless otherwise specified. All interventions and all laboratory or other diagnostic testing reflected in outcomes will be performed as part of routine clinical care. Additional details of outcome definition are included in the Appendix D.

7.2.1 Primary outcome

The primary outcome will be all-cause 28-day mortality (death on or before study day 28).

7.2.2 Key secondary outcome

The key secondary outcome will be renal replacement therapy-free days to day 28, with death on or before day 28 assigned a value of -1.[58] For patients with baseline end-stage renal failure on dialysis prior to the index hospitalization, potential values for this ordinal outcome will be 0 or -1.

7.2.3 Exploratory clinical outcomes

- In-hospital all-cause mortality
- 90-day all-cause mortality
- Vasopressor-free days to day 28
- New receipt of renal replacement therapy after enrollment (excludes subjects receiving renal replacement therapy prior to enrollment)
- ICU-free days to day 28 (calculated analogous to vasopressor-free days)
- Hospital-free days to day 28 (calculated analogous to vasopressor-free days)

7.2.4 Exploratory safety outcomes

- New-onset clinical diagnosis of acute coronary syndrome or ST elevation or non-ST elevation myocardial infarction
- New-onset clinical diagnosis of mesenteric ischemia
- New-onset clinical diagnosis of extremity, nose, or ear ischemia
- Clinical diagnosis of vasopressor extravasation
- Clinical diagnosis of clinically-significant arrhythmia (sustained ventricular tachycardia, reentrant [supraventricular] tachycardia, atrial arrhythmia with rapid ventricular response requiring intervention, or new-onset atrial fibrillation or flutter)
- Clinical diagnosis of cardiogenic shock
- Cardiac arrest
- New-onset severe hyponatremia (serum sodium <120 mEq/L) after enrollment
- Maximum lactate from enrollment through day 7

- Serum troponin above upper limit of normal from enrollment through day 7

7.2.5 Monitored care processes

Delivery of interventions for septic shock directly related to the studied intervention or which may be indirectly influenced by the intervention will be evaluated. These include:

- Study-specific threshold-based vasopressin order entered by clinical team at any time
- Receipt of vasopressin at any time after study entry
- Maximum dose of non-vasopressin vasopressors (in norepinephrine equivalents) before initiation of vasopressin. (For patients never initiated on vasopressin, value is the patient's maximum total dose of vasopressors.)
- Receipt of stress-dose steroids from enrollment through study day 7
- Volume of IV resuscitation fluid administered during the first 24 hours after enrollment
- Volume of IV resuscitation fluid administered during the first 72 hours after enrollment
- Placement of new central venous access (central venous catheter or peripherally-inserted central catheter) through study day 7

7.3 Data analysis

Patients will enter the study at the time they first meet all entry criteria at a study hospital. As described in Section 5.2.7, patients' study entry and treatment assignment for intention-to-treat analyses will be based on the date and time they meet all entry criteria at a study hospital, with all subsequent care and outcomes through the end of the index hospital encounter and study follow-up (including any subsequent episodes of shock meeting study entry criteria) contributing to the subjects' study outcomes. For an individual patient, to ensure independence of observations, any episodes of shock meeting study inclusion criteria that occur during distinct hospital encounters subsequent to the index hospital encounter will be included in safety monitoring reports for the Data and Safety Monitoring Board (DSMB, see Sections 7.6 and 10) but will be excluded from other analyses.

Full details of planned analyses will be prespecified in a Statistical Analysis Plan.

7.3.1 Descriptive and adjusted analysis

Categorical variables will be reported as number (percent). For descriptive reporting, continuous variables will be reported as mean (standard deviation) or median (25^{th}-75^{th} percentile). Between-group comparisons will, as appropriate, employ the t-test with unequal variance or the Wilcoxon rank-sum test for continuous variables and chi-squared or Fisher's exact test for categorical testing.

7.3.2 Primary analysis

The primary analysis will compare the effect of the two treatment strategies on 28-day mortality on an intention-to-treat basis using a generalized linear mixed effects model incorporating a logit link, an indicator variable for treatment strategy assignment, a random effect for study hospital (to account for within-hospital correlation), and patient-level adjustment covariates (including age, sex, source of infection suspected or diagnosed at the time of study entry [pulmonary, urinary, GI/abdominal, skin, other/multiple], preexisting kidney disease [see Appendix D], preexisting heart disease [see Appendix D], non-cardiovascular SOFA score, and initiation of vasopressors within 72 hours of hospital arrival). The generalized linear model will use a Wald test to evaluate whether we have evidence of a non-zero effect of the exposure. A two-sided p value <0.05 will be considered significant.

7.3.3 Key secondary analysis

The sole pre-specified secondary analysis will compare the effect of the two treatment strategies on renal replacement therapy-free days on an intention-to-treat basis using analysis and statistical testing methods parallel to that employed for the primary outcome, using a random effects proportional odds model with random effects for study hospital and fixed effects for covariates to evaluate the ordinal outcome.

7.3.4 Exploratory analyses

Exploratory analyses will not include adjustment for multiple comparisons and will thus be considered hypothesis generating. Pre-planned secondary analyses will:

- Evaluate the intervention's effect on exploratory outcomes using a similar statistical model as the primary analysis, including a random effect for study hospital and adjustment for patient-level covariates. Secondary analyses will replace the logit link as needed based on nature of the outcome variable.
- Using a similar statistical model as the primary analysis, including adjustment for patient-level covariates, measure heterogeneity of treatment effect for the primary outcome associated with patient-level covariates included in the adjustment model by incorporating an interaction term between covariate of interest and the treatment assignment and testing the significance of the interaction term's coefficient. Planned covariates for heterogeneity of treatment effect evaluation include: age, sex, source of infection diagnosed at the time of study entry, chronic kidney disease [see Appendix D], preexisting heart disease [see Appendix D], non-cardiovascular SOFA score, and time between hospital presentation and initial receipt of vasopressor (<72 hours vs >= 72 hours).

7.3.5 Sensitivity analyses

Pre-planned sensitivity analyses will include:

- Repeat the primary and key secondary analysis restricted to enrolled patients for whom study-specific threshold-based vasopressin order was entered;
- Repeating the primary analysis without adjustment for baseline patient covariates;
- Repeating the primary analysis adding time as a covariate. The time variable will be a continuous variable indicating study month (values from 1 to 28) and modeled using restricted cubic splines to allow for non-linearity.

7.4 Missing data

Data for the primary outcome and treatment assignment is expected to be non-missing for all patients. Missing outcome and treatment assignment data will not be imputed for any analysis. The prespecified outcome analysis model covariates are also expected to be 100% non-missing after electronic data collection supplemented by manual chart review. However, if missing data for covariates is present for >0.2% of eligible subject, we will perform the primary, secondary, and exploratory outcome analyses after imputing missing values using chained equations. An analysis based on complete cases will be performed as a sensitivity analysis for the primary and key secondary analysis. If covariate missingness is present for ≥1 eligible patient but ≤0.2% of the overall cohort, the primary analysis will be restricted to complete cases, with sensitivity analyses based on multiple imputation by chained equations performed for the primary and key secondary analysis. For descriptive data, missing data will not be imputed and complete case analysis will be used and missingness will be reported.

7.5 Sample size/power analysis

Based on historical data, the study hospitals average roughly 11.7 patients per month (range 1-45) with septic shock of whom 8.25 patients per month (range 0.3-35) receive ≥0.1 mcg/kg/min norepinephrine (or equivalent). We conservatively estimated that the study will last 16 months — including 8-12 months of enrollment at all study sites and an additional 4 month vanguard phase at the largest-volume site (see study timeline depicted in Appendix B) — and will enroll approximately 2050 patients, including approximately 1445 patients with maximum vasopressors dose ≥0.1 mcg/kg/min norepinephrine (or equivalent). Power analyses employed the following additional assumptions:

- Historical patient volumes for each cluster;
- 28-day mortality of 40% among patients receiving ≥0.1 mcg/kg/min norepinephrine (or equivalent) assigned to the higher vasopressin initiation treatment strategy (considered the control group);
- 28-day mortality of 21% for all patients (regardless of treatment assignment) receiving <0.1 mcg/kg/min norepinephrine (or equivalent);
- Within-cluster correlation of 0.003;
- Randomization stratified by hospital patient volume (see Section 4.4 and Appendix B);
- No differential impact of the intervention across clusters; and
- A type 1 error rate of 0.05.

Simulation analyses based on these assumptions estimate that the trial will have 80% power to detect a 5.4% difference in all-cause 28-day mortality (27.6% vs 33%) for the compared treatment groups (Figure 4).[59,60] The final sample size will be determined by the number of patients enrolled with septic shock during the planned trial duration, with a maximum expected enrollment of ≤7000 patients.

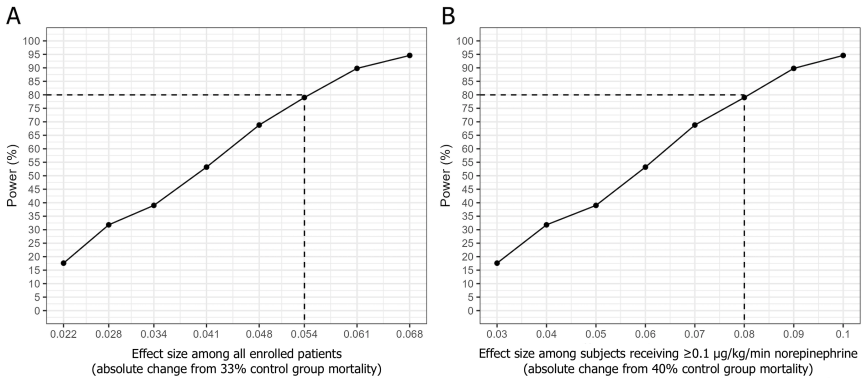

Figure 4. Power estimates for varying effect sizes applied to (A) the overall population and (B) the subset of patients receiving ≥0.1 mcg/kg/min of norepinephrine (or equivalent). Power analyses employed the assumptions described in Section 7.5, 13 clusters, and a 16-month study with monthly crossover as shown in Appendix B.[59,60]

7.6 Interim analysis

The trial DSMB will conduct interim analyses for safety approximately every six months, beginning with availability of data for patients discharged within 6 months of study initiation. In addition to monitoring safety on an ongoing basis, the DSMB will conduct a single interim analysis for efficacy including patients enrolled within the first 8 months of the trial. This analysis will employ a conservative Haybittle-Peto stopping boundary (two-sided p-value <0.001) to test for between-group differences in the primary outcome, allowing the final analysis to proceed without altering the p-value threshold for assessing statistical significance (p=0.05).[61-63] There will be no interim futility analyses, and therefore no formal interim stopping rules for futility. The decision not to include a futility analysis is based on our goal to obtain the most accurate possible effect sizes for this minimal risk study and potential for utilization rate

of study orders to influence study monthly enrollment rates in unpredictable ways. Given that both thresholds are widely practiced, ethically there is not a duty to stop the trial early based on futility.

Prior to the end of the trial, the DSMB will review non-comparative (pooled) data on (1) monthly enrollment; (2) primary outcome incidence; (3) the proportion of enrolled patients who received ≥0.1 mcg/kg/min norepinephrine (or equivalent); and (4) rates of treatment strategy crossover and non-adherence. Lower-than-expected rates of patient enrollment, the primary outcome, or shock treated with ≥0.1 mcg/kg/min norepinephrine (or equivalent) or higher-than-expected treatment strategy crossover and non-adherence could all decrease the study's power to detect the preplanned effect size. Therefore, if meaningful differences from expected values for these factors are observed and continuing the study beyond the planned duration is determined to be operationally feasible,[50-52] the DSMB may request the unblinded biostatistician re-estimate the sample size required to maintain the prespecified power to detect the prespecified treatment effect. Based on this analysis, the DSMB may recommend extending the trial beyond the planned duration and/or resuming the trial after study hospitals' EMR transition up to a maximum of 30 months of active enrollment and a maximum total trial duration of 4 years.[64]

To protect patient safety, the DSMB will have the ability to stop the trial at any time (including before or in between planned safety analyses), to require supplementary data or interim analyses, or to request study protocol revision. DSMB recommendations, including those associated with interim safety and efficacy analyses, will be at the discretion of the DSMB, and may take into account existing and newly-available evidence external to the present study as well as the totality of available data from the present study, including consideration of the p-values from interim safety and efficacy analyses along with other clinical outcomes, adverse events, and other potential clinical factors.

8. RISK ASSESSMENT

This trial is a pragmatic comparison of the effectiveness of two strategies for management of septic shock using vasopressin within the range of current usual practice and guidelines. Patients will all be closely monitored in an ED or ICU setting. This will allow for prompt treatment of any untoward events. It is further anticipated that enhanced safety monitoring using EMR queries and chart review will in fact provide even greater safety monitoring than the already high level applied in routine clinical use. Clinicians will retain and exercise their clinical judgment in the care of patients; the intervention is a default setting that applies usual clinical care in a non-biased way. The trial will be overseen by an independent Data and Safety Monitoring Board (DSMB), which will operate according to an approved charter.

8.1 Potential risks

8.1.1. Risk of vasopressin treatment for septic shock

Vasopressin, FDA-approved and marketed as both generic product and as branded VASOSTRICT™ with a labeled indication for treatment of septic shock, has been used extensively for years in clinical practice. Vasopressin, at the infusion rates and indications studied within this trial, is in common clinical use across study hospitals. The only contraindication to vasopressin administration is allergy to vasopressin or its vehicle. At doses substantially higher than will be used in the present septic shock treatment strategies, vasopressin has been associated with bradycardia and decreases in cardiac output. Based on passive reporting (as specified in the package insert) and general observations in the literature, "the most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital)." It is anticipated that low, fixed-rate infusions—the clinical standard at study hospitals—are well tolerated without adverse reactions; in common clinical use, no special precautions or monitoring are used for vasopressin as opposed to other vasopressors. The trial in no way proposes or implements a change in the infusion rates of vasopressin; the locus of randomization is *when* the vasopressin infusion should be initiated.

8.1.2. Risk of lower versus higher thresholds for vasopressin initiation

Comparison of the risks and benefits of lower versus higher thresholds is the purpose of the present trial. Because both lower and higher thresholds are routinely encountered in clinical care, with variation in use driven by factors unrelated to patient attributes, the theoretical risks and benefits of lower versus higher thresholds for vasopressin initiation are already features of usual care in the clinical environment.

8.1.3 Risk of confidentiality breach

Potential consequences of a breach of confidentiality to the subject could include identity theft, loss of privacy, theft, embarrassment, or harassment. This risk is extremely low and will be managed intensively by study personnel.

8.2 Alternatives to participation

While randomization is at the level of ICU rather than patient, treating clinicians retain the ability to not prescribe or administer vasopressin at all or to prescribe and administer vasopressin at thresholds other than those evaluated in this trial.

8.3 Minimization of risks

Federal regulations 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. This trial meets those requirements, incorporating numerous mechanisms to minimize risks to patients. The trial protocol includes manual and electronic query-based safety monitoring, solicited reporting of potential protocol-related adverse events, and routine monitoring by an independent DSMB empowered to require stopping the trial or modification of the trial protocol at any time. Data privacy and confidentiality will be intensively managed in accordance with Intermountain Health's high-reliability methods and processes.

8.3.1 Protections against altered clinical risk/benefit from vasopressin strategies

Both tested strategies are within the spectrum of care provided to thousands of patients per year at study hospitals (see Figure 1) and to hundreds of thousands of patients nationwide each year.[43] Conditional on the clinician's decision that a patient should receive vasopressin if their response to first-line vasopressors is inadequate, the study essentially aims to compare the effects of implementing two alternative guidelines providing (compared to current guidelines) more definitive recommendations regarding the threshold for adding vasopressin to first-line vasopressors for septic shock. As such, the pragmatic intervention explicitly encourages clinicians to use their clinical judgment for individual patients to including assessment of whether patient factors require (1) choosing an alternative threshold for starting vasopressin or (2) not prescribing vasopressin. Clinician education delivered prior to study launch and refreshed at intervals during study conduct will address this topic and include discussion of conditions that have potential to alter risk/benefit for vasopressin based on prior evidence or pathophysiologic consideration. In addition, in the presence of patient factors that may alter the risk/benefit profile of vasopressin, EMR-based logic will suppress delivery of prompts to clinicians to consider use of study-specific threshold-based vasopressin orders (see Section 5.2.2.3 and Appendix C).

8.3.2 Protections in setting of potential allergy to vasopressin or its vehicle

Vasopressin is an endogenous hormone, and allergy or adverse event history to the drug or its vehicle is expected to be rare. We were unable to identify any reports of vasopressin allergy in the medical literature as of November 2022. Study hospitals employ a shared electronic medical record with embedded allergy/adverse event checking and decision support during medication electronic order entry. These mechanisms will notify ordering clinicians of potential vasopressin allergy/adverse event at the time of order entry and prevent completion of order for vasopressin unless — as per usual practice — clinician specifically and intentionally overrides based on clinical judgement. We anticipate that these robust mechanisms will prevent administration of vasopressin to patients in whom an allergy is present.

8.3.3 Protections against loss of privacy or breach of confidentiality

Protection of participant identity and prevention of unintentional release of protected information is of paramount importance to the study team.

- *Data storage and transfer*: Data will be maintained in password-protected, encrypted research servers, REDCap (a secure, HIPAA-compliant system), or password-protected, encrypted computers. Intermountain Health deploys comprehensive information technology support systems to maintain and regularly update computer systems and maintain physical and electronic safeguards for data management. Any paper case report forms will include minimal identifiers and will be stored in secure locations.
- *Data access*: Only the PI, co-investigators, and the study team will have access to identifying information. All individuals with access to identifiable data will have all necessary human subjects training and, as applicable, Good Clinical Practice training.

- *Training*: All study personnel will maintain appropriate training in human subjects research and data protection. The PI, co-investigators, and study staff responsible for study coordination, data collection, and data management of the associated clinical trial will maintain Good Clinical Practice training.
- *Certificate of Confidentiality*: A Certificate of Confidentiality as described in subsection 301(d) of the Public Health Service Act (42 U.S.C 24) will be obtained from the National Institutes of Health. The Certificate of Confidentiality will protect the privacy of research participants by prohibiting disclosure of identifiable information compiled for purposes of the trial (e.g., in response to legal subpoena) without consent of the individual identified except as required by Federal, State, or local laws or for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

8.3.4 Incidental findings

Data review and analysis will use only data collected as part of routine clinical care and operations. We therefore do not expect identification of new incidental findings relevant to patient care.

8.4 Potential benefits of the proposed research to human subjects and others

Study subjects may or may not receive any direct benefits from their participation in this study. It is unclear whether a lower (versus higher) threshold for initiating vasopressin as a secondary vasopressor in septic shock will provide benefit. Thus, the optimal treatment is undefined at this point. This study has the potential to generate important findings for patients with sepsis and their treating clinicians, including optimal strategies for vasopressor management in septic shock. The risks to patient confidentiality and the risks for adverse drug reactions appear substantially less than the potential benefit to sepsis patients and the important knowledge gained about delivery of septic shock care.

8.5 Importance of the knowledge to be gained

Patients with sepsis —a syndrome defined by infection associated with acute organ dysfunction — have high mortality. Septic shock is a common reason for ICU admission with even higher mortality. Optimal strategies for management of patients who receive more than low doses of vasopressors to achieve target blood pressure are unclear. The overall hypothesis of this pragmatic comparative effectiveness trial is that a lower (versus higher) threshold for starting vasopressin as a secondary vasopressor is associated with improved clinical outcomes. Based on the preceding assessment of risks and potential benefits, the risks to subjects (no more than minimal risk) are acceptable in relation to anticipated knowledge to be gained to improve care for the common and deadly sepsis syndrome.

9. HUMAN SUBJECTS

We will prospectively assess the effect of septic shock treatment strategies encouraging a lower versus higher threshold for initiating vasopressin as a secondary vasopressor. In this pragmatic, embedded, comparative effectiveness trial, strategies will be implemented at the hospital level, and patients with septic shock will be exposed to the treatment strategy in place at the study hospital at the time they initiate vasopressors, with patients' treating clinicians exercising clinical judgment as to whether to apply a study strategy to any individual patient.

9.1 Selection of subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. All eligible patients will be enrolled. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

9.2 Waiver of informed consent and HIPAA authorization

Recognizing feasibility, generalizability, methodological integrity, and appropriate ethical precedents, we will request a waiver of informed consent and HIPAA authorization based on the following criteria as per 45 CFR 46.116(f) and the HIPAA Privacy Rule. Numerous previous randomized trials comparing two or more strategies or treatments within standard of care for critically ill and other hospitalized patients have been completed under a waiver of informed consent.[53,54,65-84]

9.2.1 Research involves no more than minimal risk

Vasopressin is recommended as a preferred second-line vasopressor in septic shock, but the threshold for adding this agent to first-line vasopressors varies widely between patients and — demonstrating practice variation not driven by patient factors — across hospitals. The planned trial will compare two strategies for vasopressin initiation that fall within the range of practice commonly used in routine clinical care. Both are strategies to which patients could be exposed even if not participating in the study. No established differences in risk and benefit are known to exist between the two approaches based on the currently available data. Clinicians will be free to deviate from the assigned strategy based on clinical judgement. If a clinician feels an individual patient will benefit from starting vasopressin at a lower threshold, the clinician will be permitted to start vasopressin at a lower threshold regardless of group assignment. If a clinician feels that an individual patient will benefit from starting vasopressin at a higher threshold, the clinician will be permitted to start vasopressin at a higher threshold regardless of group assignment. Thus, the only patients for whom the study-defined treatment strategy will determine the threshold at which vasopressin is started are those patients for whom treating clinicians feel that either of the study's two vasopressin initiation thresholds is consistent with safe and effective care for that patient. The approach taken by the VASSPR trial — replacing the arbitrary exposure to competing, unproven therapies seen currently with vasopressin with structured variation created by randomization[85-87] — is a well-accepted strategy recently adopted in numerous other "embedded pragmatic clinical effectiveness trials" to answer important clinical questions in critical care medicine[53,54,73-80] specifically and both inpatient[81-83] and outpatient[84,88-91] medicine generally.

9.2.2 No adverse effects on the rights and welfare of participants

Exposure to (1) structured variation within the range of accepted and observed usual care — rather than arbitrary variation — with regard to initiation of secondary vasopressors and (2) research team abstraction and analysis of data routinely collected in the course of clinical care should have no adverse

effects on the rights or welfare of study subjects. Because risk is minimal given this design, the waiver of consent and authorization will not adversely affect the rights or welfare of subjects.

9.2.3 The research could not practicably be carried out without waiver of informed consent

Conceptually, this trial compares outcomes associated with adoption of two different guidelines for secondary vasopressor initiation in septic shock. Delivery of the two different treatment strategies will therefore be integrated within usual care via the kinds of implementation methods used in real-world practice to standardize clinical care and aid adoption of new guidelines. These implementation methods target groups of physicians, nurses, and pharmacists at the unit/hospital level rather than targeting at the level of individual patients. The trial's underlying question and intervention deployment strategies therefore require use of an embedded, cluster-randomized trial design rather than individual patient randomization. As a result, while clinicians are empowered to individualize vasopressor management for each patient as needed, all patients treated with vasopressors for septic shock at a study hospital will be exposed to the vasopressin treatment strategy assigned for that month at that hospital. It would be impracticable and unethical, violating core principles of informed consent, to require patients to choose between giving informed consent for trial participation or transferring to another hospital before starting treatment for septic shock, especially since vasopressor initiation for critically ill adults is a time-sensitive procedure for which delay increases the likelihood of life-threatening hemodynamic compromise. Restricting study enrollment and analysis to strategy-exposed patients capable of providing consent — a non-representative subset of all strategy-exposed patients due to the condition's high mortality rate and frequent association with impaired mental status/decisional capacity — would compromise the scientific validity of the study. In summary, because of these considerations, this research could not practicably be carried out without the waiver of consent.

9.2.4 Information on the trial will be available to all ICU patients

We will make available patient information sheets describing the trial in lay language via distribution in study ICUs to all ICU patients. Information sheets may be posted or distributed in public areas of the ICU (e.g. waiting room), core entryways, and/or included in information packets provided to patients and their families. Posters with general information on the study may also be displayed in patient rooms and/or public areas of the ED and ICU. Providing information specifically to patients enrolled in the study (such as the time of meeting entry criteria) is not feasible given the pragmatic, distributed nature of the intervention across 13 hospitals, likelihood that many patients will have passed away or not be at a home address at time of retrospective query-based eligibility identification, and risk that attempting to contact patients would substantially increase the risk of a confidentiality breach.

9.2.5 The minimal necessary amount of protected information will be obtained

Only data necessary for the completion of the study will be collected. The patient ID, encounter ID, social security number, address, and date of birth are necessary to allow data linkage and identification of the specific patient encounter for supplemental data abstraction. Event date/times are necessary for care process and outcome measurement, including calculation of the elapsed time related to various patient management actions.

9.2.6 All data, including PHI, will be securely guarded from improper disclosure

High-level safeguards will be in place to protect subject identity and confidential data. The study data will be kept on encrypted, password-protected computers. These computers are routinely used for storage of patient data and research data including subject identifiers. The data will only be accessible to members of the research team, and all members of the research team have completed Human Subjects

Protections and understand the importance of protecting subject privacy and confidentiality. Protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by under applicable regulations. Minimal identifiers will be maintained linked to the data. Maintaining minimal identifiers linked to the data is necessary to allow (1) manual abstraction of additional data from the electronic medical record and (2) potential future linkage – with IRB approval – of the data to additional datasets. No individual subject data will be presented in any presentation, publication or report related to this research. Data will be presented only in anonymized or aggregate form or as results of statistical analyses and will not include any individual-level data that could be traced to a particular subject.

10. SAFETY AND DATA MONITORING AND REPORTING

10.1 Summary and rationale for safety and data monitoring and reporting

The study PIs and steering committee will be responsible for data and safety monitoring associated with achieving the study objectives. The VASSPR trial will be overseen by an independent Data and Safety Monitoring Board (DSMB). The DSMB —comprised of independent individuals with expertise in critical care medicine, sepsis, biostatistics, clinical trial design and conduct, and clinical trial ethics — will operate according to an approved charter.

Assuring patient safety is an essential component of this clinical trial. The approach to data and safety monitoring and assessment within this trial reflects attributes of the studied treatment strategies and the target population and the environment in which study subjects will be receiving care.[92]

- Vasopressin is a mature, FDA-approved, and widely-marketed therapy for septic shock with which there is extensive experience. Treatment of septic shock with vasopressin as a second-line vasopressor generally and the tested strategies involving alternative threshold for vasopressin initiation specifically are in common clinical use both across the United States and at the study hospitals. Vasopressin has a labelled indication for septic shock and its use in the present study is consistent with the range of practice observed in the U.S. and at study hospitals. It is anticipated that low-dose, fixed-rate infusions—the clinical standard at study hospitals—are well tolerated without adverse reactions; in common clinical use, no special precautions or monitoring are used for vasopressin as opposed to other vasopressors.
- The study intervention involves randomization to one of two “default strategies” for initiation of secondary vasopressors in septic shock. If treating clinicians believe an alternative approach to shock management is preferable for an individual patient at any point in their care, clinicians will be able to select the management approach that the treating clinicians judge to be best.
- Patients with septic shock are critically ill and may be reasonably anticipated to experience multiple adverse events (AEs) regardless of any study procedures.
- Clinical care for study subjects will occur in clinical settings dedicated to provision of highest-acuity clinical care and within the context of routine clinical care for a high-acuity procedure (vasopressor administration) employed to treat septic shock. Characteristics of routine care while on vasopressor therapy include:
    - Care by a critical care, emergency medicine, or other appropriately trained nurse with a low patient-to-nurse staffing ratio.
    - ED patients have immediate access to an ED provider, while ICU patients will have immediate access to an in-house physician as well as either direct access to an in-house critical care physician or telemedicine-based access to a critical care physician.
    - Routine clinical care for septic shock patients will — independent of any study procedures — involve continuous or frequent monitoring of blood pressure and other vital signs via invasive or non-invasive means as well as frequent monitoring of physical exam, symptoms, and laboratory parameters.

Given these considerations, trial safety monitoring will combine careful monitoring via chart review and electronic queries with a focus on potential adverse effects identified from vasopressin product labeling and prior clinical trials and active surveillance via event reporting by bedside clinical personnel. Also consistent with these considerations, investigator AE review will not take place except for AEs which clinical personnel flag as potentially related to study procedures, and narrative-based AE reporting will not take place unless review by the research team finds event is both possibly, probably or definitely

related to study procedures and either (1) serious or (2) suggests the research places subjects or others at a greater risk of harm than was previously known or recognized.

10.2 Potential Risks and Benefits for Participants

- Potential risks: The risk level associated with this study is estimated to be no more than minimal, since the studied septic shock management strategies are in common clinical use across study hospitals prior to the study. The pragmatic intervention will replace arbitrary variation with structured variation by mimicking implementation of a care guideline or recommendation for vasopressin initiation timing with a clearer threshold for starting vasopressin than is currently available while preserving clinicians' ability to apply clinical judgement and select treatment approaches outside the suggested strategies for individual patients as deemed necessary. See Section 8.3.1 for additional details.
- Potential benefits: Study subjects may or may not receive any direct benefits from their participation in this study. This study has the potential to generate important findings for patients with sepsis and their treating clinicians, including optimal strategies for vasopressor management in septic shock. See Section 8.4 for additional details.

10.3 Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of patients in the clinical trial that will test septic shock strategies involving two default thresholds for vasopressin initiation.

10.3.1 DSMB membership

The DSMB will consist of members independent of the clinical trial with expertise in critical care, sepsis, biostatistics, clinical trial design and conduct, and clinical trial ethics.

10.3.2 DSMB responsibilities

The DSMB will make recommendations to the principal investigator (PI) and trial steering committee with respect to:

- Review and approve the research protocol and plans for data and safety monitoring;
- Protect the safety of the study participants, including review of safety outcomes and adverse events during routinely scheduled meetings and at other intervals as needed;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual, participant risk versus benefit, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the principal investigator (PI) or their delegate;
- Make recommendations to the PI and trial steering committee concerning continuation, termination or other modifications of the trial;
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the IRB by commenting on any concerns related to study conduct, enrollment, sample size, and/or data collection.

The PI will be responsible for the preparation of all DSMB and adverse event reports. DSMB recommendations — including recommendations to end, modify, or continue the trial — will be

communicated to the PI in writing (paper or electronic). The PI will be responsible for sharing these recommendations with the IRB.

10.3.3 DSMB meeting frequency

The DSMB will meet prior to initiation of the clinical trial to review the trial protocol and plan for monitoring study progress and safety measures. Approval by the DSMB and Institutional Review Board (IRB) will be required prior to initiation of the clinical trial. After trial initiation, the DSMB will meet approximately every six months to review study progress and safety data. The DSMB may convene additional *ad hoc* meetings as needed upon determination of the DSMB chair, either alone or in consultation with the trial PI and/or trial steering committee. An interim efficacy analysis will be conducted after primary outcome data are available for the primary outcome for patients enrolled through the end of study month 14. There will be no futility analysis.

10.3.4 Conflict of interest for DSMB

The members of the DSMB will have no direct involvement with the study investigators or intervention related to the trial outside of DSMB meetings and other DSMB-related communications. DSMB members will provide a Conflicts of Interest Disclosure which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to study objectives.

10.4 Adverse Event Definitions

- **Adverse event** — A clinical trial adverse event is any untoward medical event temporally associated with the research participation and which is not tracked as a clinical outcome, whether or not it is considered related to a drug or study procedure.

- **Seriousness:** A ***serious adverse event (SAE)*** is any AE that results in any one or more of the following outcomes:

    - Death
    - A life-threatening experience (that is, immediate risk of dying)
    - Event requiring inpatient hospitalization or prolongation of existing hospitalization.
    - Persistent or significant disability or incapacity.
    - Congenital anomaly or birth defect
    - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

- **Unanticipated adverse events:** An adverse event that, in the judgment of the study principal investigator or their delegate, is out of the range of that typically observed in terms of nature, severity, or frequency for the patient's underlying critical illness, septic shock, and baseline medical conditions/health.

  Unanticipated adverse events that are also serious and are judged to be possibly, probably, or definitely related to study procedures will be classified as a ***serious unanticipated suspected adverse reaction (SUSAR)***.

- **Unanticipated problem (UP):** Any incident, experience, or outcome that in the judgment of the study principal investigator or their delegate meets all of the following criteria:
  - Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures; and (b) the characteristics of the subject population being studied, including the anticipated course of subjects' critical illness and septic shock and their associated conditions and predisposing risk factors;
  - Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
  - Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.5 Adverse Event Monitoring and Reporting

Patients eligible for this study are critically ill and at high risk of death, serious organ dysfunction requiring intervention, prolonged hospitalization, or other adverse outcomes. Study personnel have defined a system to collect, review, and closely monitor clinical outcomes and adverse events appropriate to patients' baseline risk, the nature of the study intervention, the pragmatic trial design, the study's planned methods for data collection, and the environment in which patients will receive care (Figure 5). Safety outcomes and potentially reportable adverse events will be identified via a combination of electronic queries of the medical record, structured manual review of the electronic medical record by trained study personnel, and collection of reports of suspected adverse reactions from bedside clinical personnel. Consistent with established procedures in both traditional and pragmatic trials enrolling critically ill patients, investigator review and adjudication will focus on events flagged by research or clinical personnel as potentially related to study procedures.[93]

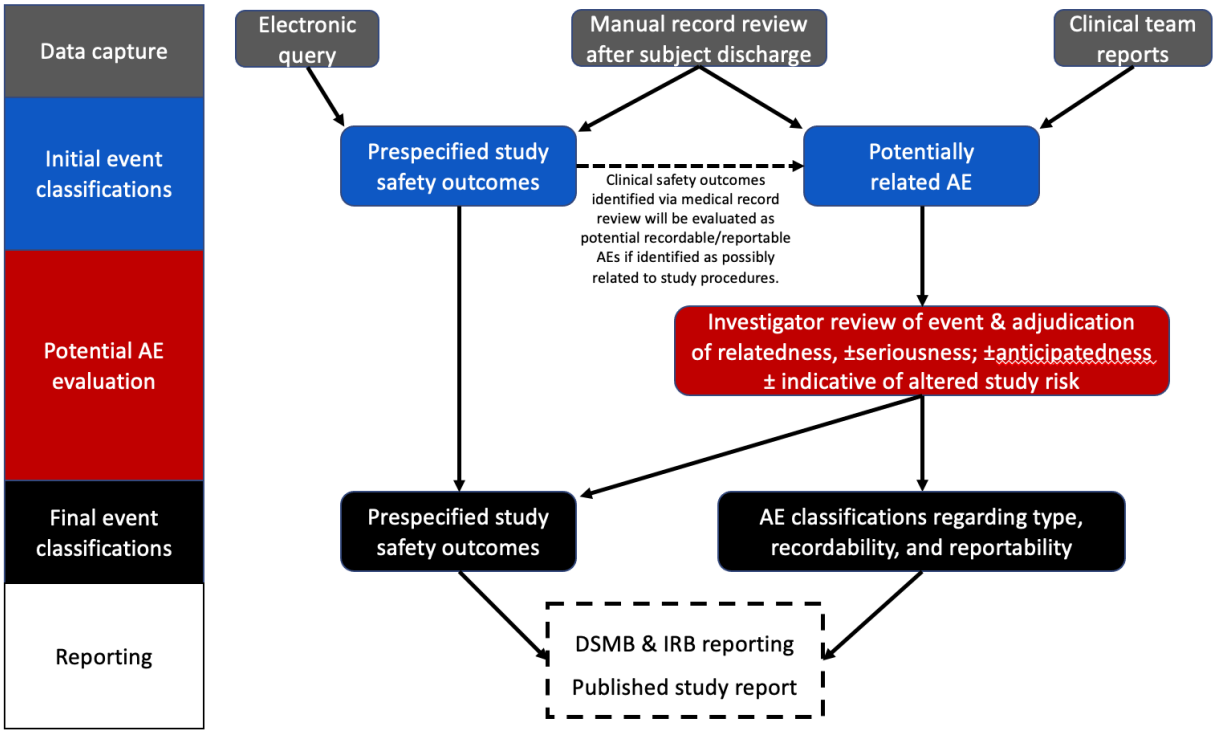

Figure 5. AE monitoring schema for VASSPR trial.

10.5.1 Prespecified study safety outcomes

A prespecified list of clinical outcomes will be systematically collected via electronic queries and manual review of the electronic medical record (see Section 7.2) for all study subjects. Data on study safety outcomes as well as hospital mortality will be reviewed for enrolled subjects at scheduled meetings of the study DSMB unless events meet reportable adverse event criteria described below.

10.5.2 Anticipated clinical events (not considered adverse events)

Anticipated clinical events are adverse events consistent with subjects' septic shock and underlying critical illness and preexisting or concurrent medical conditions. Anticipated clinical events will be collected in the study data and included in study clinical outcomes as appropriate. Anticipated clinical events will not be considered reportable adverse events unless the event is considered by the study team to be possibly, probably, or definitely related to study procedures.

The following is a partial list of adverse events that, through end of study follow up, will be considered anticipated clinical events that will be captured as clinical outcomes:

- Death (all deaths will be captured as part of routine data collection)
- Progressive, persistent, or recurrent shock
- New, secondary, or healthcare associated infections
- New, persistent, or progressive organ dysfunction or failure (and any associated symptoms, signs, and interventions) including but not limited to:
    - Cardiac failure (including heart failure, cardiac arrest, progressive or recurrent shock with or without receipt of vasopressors)
    - Cardiac arrhythmias
    - Myocardial injury or infarction
    - Liver injury, dysfunction, or failure

    - Acute kidney injury or failure, including laboratory abnormalities or treatment with renal replacement therapy
    - Hematologic abnormalities (e.g. thrombocytopenia, coagulopathy, bleeding or hemorrhage, clotting [including arterial and venous thromboembolism])
    - Gastrointestinal system symptoms or dysfunction (e.g. vomiting, ileus, bowel obstruction, constipation, bleeding)
    - Respiratory symptoms, dysfunction, or failure, including use of supplemental oxygen or non-invasive or invasive respiratory support
    - Neurologic dysfunction or injury (e.g. delirium, disability, physical or cognitive impairment, ischemic or hemorrhagic stroke, and seizure)
    - Endocrine dysfunction
- New or progressive global weakness, fatigue, or physical impairment (e.g. critical illness myopathy, inability to perform previous level of cognitive or physical function or self care)
- New or progressive focal or generalized pain
- New or exacerbated psychiatric symptoms or diagnoses, including depression, anxiety, and PTSD
- Skin breakdown, rash, pressure ulcers.
- Co-interventions for treatment and monitoring (e.g. ICU antibiotic therapy, blood transfusion, arterial line placement)
- Collection, measurement, abnormalities, or alterations of clinically-collected assessments including:
    - All values for vital signs (e.g. Glasgow Coma Scale score, temperature, respiratory rate, oxygen saturation)
    - Physical exam
    - Patient history/symptoms
    - All laboratory testing and results (e.g. hematocrit, chloride, hepatitis testing)
    - All microbiologic testing and results
    - All diagnostic/radiologic testing and results (e.g. echocardiogram, HIDA scan, chest X-ray, sleep study)
- Duration of treatments and interventions (e.g. vasopressor days, ICU length of stay)
- Prolonged hospitalization or ICU stay
- Occurrence and duration of readmission to ED, hospital and/or ICU and associated diagnoses, care, investigations, and treatments

10.5.3 Reportable adverse events

For purposes of the present trial, a **reportable adverse event** is any event that in the judgment of the study PI or a qualified co-investigator is possibly, probably, or definitely related to study procedures. Adverse events that do not meet this definition will not be separately recorded or reported.

10.5.4 Adverse event reporting

The PI will report (1) SAEs that are possibly, probably, or definitely related to study procedures, (2) UPs, and (3) SUSARs to the DSMB and IRB within 7 calendar days after identification of the event. Narrative reports for these events will be anonymized and will include the nature of the event (including any interventions or treatments), its onset and cessation, outcome, and the principal or delegate investigator's opinion regarding the event's anticipatedness and the relationship between study procedures and the event. AEs not qualifying for narrative reporting will be reported in aggregate form as part of regularly-scheduled semiannual reports to the DSMB and annual reports to the IRB (Figure 6).

	Unanticipated and related and indicative of altered risk	Unanticipated and related but not indicative of altered risk	Related but not unanticipated	Not related
Serious	SUSAR and UP 7 calendar day narrative reporting	SUSAR 7 calendar day narrative reporting	Related SAE 7 calendar day narrative reporting	Non-reportable AE, safety outcome, or anticipated clinical event
Not serious	UP 7 calendar day narrative reporting	Unanticipated & related AE, routine aggregate reporting	Related AE, routine aggregate reporting	

Figure 6. AE event classification and reporting.

AE reports and annual summaries will not include subject- or group-identifiable material. Data will be presented in a blinded manner during open sessions involving the DSMB. At meetings with the DSMB or in IRB reports, data and discussion are confidential. Participant identities will not be known to the DSMB or to the IRB.

10.6 Enrollment, procedure, regulatory, and data quality monitoring

The trial data monitoring plan will include

1. Review of accrued data (including AEs) at monthly meetings of the study protocol committee;
2. Monitoring of data quality and interim safety and data analysis performed by the DSMB;
3. Semi-annual audits of study materials by the regulatory affairs group;
4. An annual review performed by the responsible IRB.

Careful monitoring of the data collection, regulatory adherence, data quality, and study procedures will help to protect the safety of study subjects, the quality of data, and the integrity of the study. The PI or study staff will review all data collection on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data verification for key demographic, exposure, and outcome parameters will be performed on an ongoing basis for a random 5% of all trial subjects. This will occur on the basis of data reabstraction by someone other than the individual who originally collected the data or by blinded duplicate data entry. The results of the ongoing data review will be incorporated into each review with the DSMB. A statement reflecting the results of the ongoing data review will be incorporated into the annual report for the IRB.

10.7 Frequency of data and safety monitoring

The PI and study team will review data quality and adverse event reports monthly and meet with the DSMB approximately every 6 months, either in-person or by teleconference call, to review study progress, data quality, and participant safety data. A summary report on all adverse events and data quality will be submitted to the IRB during annual recertification as per IRB guidelines.

11. AMENDMENT HISTORY

Protocol version and date	Description of change and brief rationale	Sections
Version 1.0 (23 January 2024)	N/A	N/A [Original protocol]
Version 1.1 (17 May 2024)	Clarify that norepinephrine doses referenced throughout the protocol and employed during clinical care at study hospitals represent norepinephrine base and specify that study hospitals employ the bitartrate formulation of norepinephrine in accordance with 2024 SCCM/ESICM position paper addressing these issues. [18]	Section 3.2 Section 4.1 Appendix A
	Provide detailed calculation methods for the ICU-free days exploratory clinical outcome.	Appendix D
	Clarify methods for calculation of the hospital-free days exploratory clinical outcome when patients are discharged alive.	Appendix D
	Clarify vasopressor-free and renal replacement therapy-free day definitions by naming the described method for outcome calculation as the “last off” method.	Appendix D
	Correct date of protocol version 1.0 in amendment history table.	Section 11
	Apply consistent terminology for secondary vasopressor strategy evaluation.	Section 2 (background) Section 2 (hypothesis) Section 3.8 Section 4.8 Sections 8.4-8.5 Sections 9 Sections 9.2.2-9.2.3 Section 10.1
	Format exploratory outcomes to precisely match descriptions registered on ClinicalTrials.gov prior to trial initiation.	Section 2 (exploratory outcomes) Sections 7.2.3-7.2.4

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APPENDIX A — Eligible vasopressor and associated equivalencies

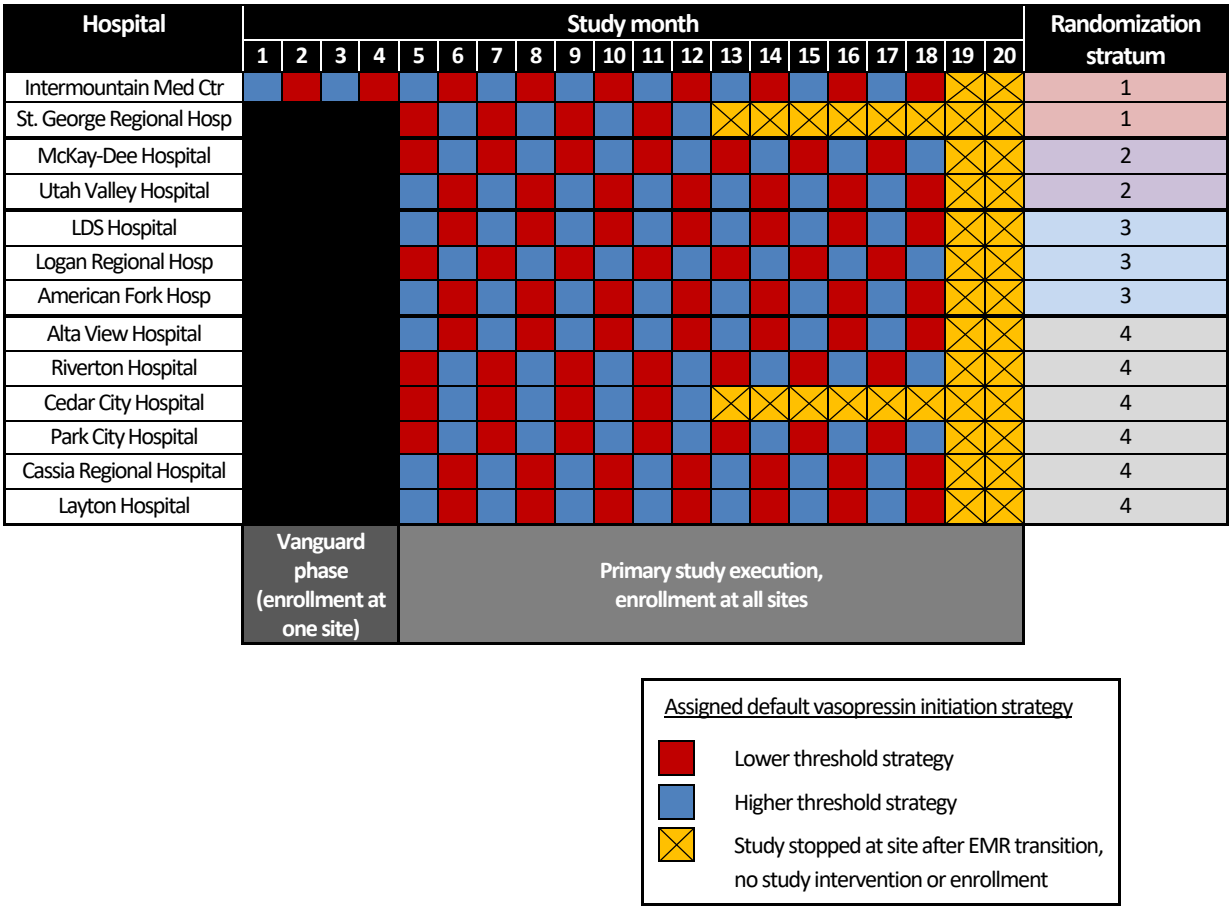
Eligible vasopressors	Multiplier (conversion factor) to convert to norepinephrine base equivalents*	Equivalent doses*	
		Norepinephrine†	Other drug
Norepinephrine†	1	0.1 mcg/kg/min	N/A
Epinephrine	1	0.1 mcg/kg/min	0.1 mcg/kg/min
Dopamine	0.01	0.1 mcg/kg/min	10 mcg/kg/min
Phenylephrine	0.1	0.1 mcg/kg/min	1 mcg/kg/min
Vasopressin	3.333333334 0.055555556	0.1 mcg/kg/min	0.03 units/**min** 1.8 units/**hr**
Angiotensin II	10	0.1 mcg/kg/min	0.01 mcg/kg/min

* Adapted from: Goradia *et al*. Vasopressor dose equivalence: A scoping review and suggested formula. *J Crit Care*, 61; 2021: 233-240.

† Norepinephrine doses represent norepinephrine base.[18]

APPENDIX B —Randomized monthly strategy assignments and example trial timeline

Initial randomization sequence is pre-determined as shown. Each individual study hospital will be assigned the lower and higher vasopressin initiation strategies for an equal number of months. A potential hospital-level study timeline is shown. The time at which hospitals exit from the study will be based on the timing of each hospital's EMR transition as discussed in section 4.5.



*

APPENDIX C — Conditions potentially altering vasopressin risk/benefit ratio

While there are no absolute contraindications to vasopressin administration other than theoretical allergy, listed conditions are noted as part of just-in-time education included within the order set for septic shock and, if identified via the EMR, result in "silencing" of the order set utilization reminder when vasopressors are ordered outside the septic shock order set for patients on antibiotics.

Condition	Method of identification for silencing	Rationale
Severe hyponatremia	Serum sodium <120 mEq/L	Potential exacerbation due to osmoregulatory effects of vasopressin.
STEMI	Condition listed as active problem in EMR	Possible exacerbation due to peripheral vasoconstriction by vasopressin.
NSTEMI	Condition listed as active problem in EMR and serum troponin >10 ng/mL	Possible exacerbation due to peripheral vasoconstriction by vasopressin.
Digital, limb, extremity, nose, ear, or other soft tissue ischemia	Condition listed as active problem in EMR	Possible exacerbation due to peripheral vasoconstriction by vasopressin.
Bowel or mesenteric ischemia	Condition listed as active problem in EMR	Possible exacerbation due to peripheral vasoconstriction by vasopressin.
Pregnancy	Pregnancy or related condition listed as active problem or hCG level above upper limit of normal	While vasopressin is used in practice, unknown pregnancy-related effects of vasopressin.
Nursing mother	Related condition listed as active problem in EMR	Unknown effects on breast milk production and unknown secretion into breast milk.
Systemic sclerosis	Condition listed as active or chronic problem in EMR	Potentially higher risk of digital ischemia in setting of treatment with pure peripheral vasoconstrictor
CREST syndrome	Condition listed as active or chronic problem in EMR	Potentially higher risk of digital ischemia in setting of treatment with pure peripheral vasoconstrictor
Raynaud syndrome	Condition listed as active or chronic problem in EMR	Potentially higher risk of digital ischemia in setting of treatment with pure peripheral vasoconstrictor

Abbreviations: EMR, electronic medical record; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction;

APPENDIX D — Definitions of study outcomes and variables

Outcomes

Vasopressor-free days: Defined as the number of days alive and off vasopressor support from the time of trial enrollment to study day 28.[94,95] If a patient returns to vasopressor support and subsequently achieves vasopressor independence prior to day 28, vasopressor-free days will be counted from the end of the last period of vasopressor support to day 28 (the "last off" method). Patients discharged alive and off vasopressors will be assumed to remain vasopressor free through study day 28. Patients discharged alive and on vasopressors before day 28 will be assumed to remain on vasopressors through study day 28. A period of vasopressor dependence during a surgical procedure will not count against the vasopressor-free days calculation. If a patient was receiving vasopressors at day 28, vasopressor-free days will be zero. If a patient dies on or before day 28, vasopressor-free days will be -1.[95] The maximum number of vasopressor-free days for a patient is 28 which would be assigned if they were vasopressor independent on the day following study enrollment and remained alive meeting the definition of vasopressor independence to day 28.

Renal replacement-free days: Defined as the number of days alive and off renal replacement therapy — including intermittent hemodialysis, hemofiltration, or ultrafiltration; slow continuous ultrafiltration or dialysis; or continuous venovenous hemodialysis, hemofiltration, hemodiafiltration, or hemofiltration — from the time of trial enrollment to study day 28.[94,95] If a patient resumes renal replacement therapy and subsequently achieves renal replacement therapy independence prior to day 28, renal replacement therapy-free days will be counted from the end of the last period of renal replacement therapy to day 28 (the "last off" method). Patients discharged alive and off renal replacement therapy will be assumed to remain off through study day 28. Patients discharged alive on renal replacement therapy will be assumed to remain on renal replacement through study day 28. If a patient was receiving renal replacement therapy at day 28 or has end stage renal disease treated with hemodialysis prior to the index hospitalization, renal replacement therapy-free days will be zero. If a patient dies on or before day 28, renal replacement therapy-free days will be -1.[95] The maximum number of renal replacement therapy-free days for a patient is 29 which would be assigned if they were renal replacement therapy independent on the day of study enrollment and remained alive meeting the definition of renal replacement therapy independence to day 28.

Hospital-free days: Defined as the number of days alive and out of the hospital through study day 28. Value of outcome will be calculated analogous to vasopressor-free days, with patients who die on or before study day 28 assigned a value of -1 and patients still hospitalized on day 28 assigned a value of 0. Patients discharged to another acute care hospital (excluding psychiatric inpatient facility) or a long-term acute care facility will be assumed to remain hospitalized through study day 28. Patients discharged alive and who do not die on or before study day 28 will be assumed to remain out of the hospital through day 28.

ICU-free days: defined as the number of days alive and out of the ICU through study day 28. The value of the outcome will be calculated analogous to vasopressor-free days, with patients who die on or before study day 28 assigned a value of -1 and patients still hospitalized on day 28 assigned a value of 0. If a patient returns to the ICU and subsequently achieves ICU independence prior to day 28, ICU-free days will be counted from the end of the last period of ICU care to day 28 (the "last off" method). Patients discharged alive and who do not die on or before study day 28 will be assumed to remain out of the ICU through day 28.

Receipt of stress-dose steroids: While receiving vasopressors, any medication administrations of:

- IV hydrocortisone 50-100 mg;
- During any shortage of IV hydrocortisone occurring during the study period requiring therapeutic exchange of other corticosteroids in place of hydrocortisone at study hospitals, either:
  - Administration of fludrocortisone plus administration of an alternative corticosteroid at a dose consistent with institutional medication substitution guidelines (e.g., IV dexamethasone 8 mg or IV methylprednisolone 40 mg); or
  - Administration of an alternative corticosteroid at a dose consistent with institutional medication substitution guidelines (e.g., IV dexamethasone 8 mg or IV methylprednisolone 40 mg IV) plus no indication in medical record that corticosteroid was administered for an indication other than septic shock.

Volume of IV resuscitation fluids: Measured as the total volume of crystalloid fluids (normal saline, lactated Ringer's solution, PlasmaLyte®) or normal bicarbonate (150 mEq/L sodium bicarbonate in 5% dextrose solution or sterile water) administered at a rate of >150 ml/hr plus the volume of any IV albumin (5% or 25%) administered.

Other variables

Baseline creatinine: Baseline creatine will be obtained using an adaptation of a previously described hierarchical method.[54,96] If available, the lowest serum creatinine ≥24 hours and ≤1 year prior to hospital arrival will be used. If this data is unavailable, the lowest serum creatinine >1 year and ≤2 years prior to hospital arrival will be used. If there is no serum creatinine value available in either of these two windows, a baseline creatine may be estimated using the following formula[97]:

$$\text{Creatinine} = 0.74 - 0.2\ (\text{if female}) + 0.08\ (\text{if race is Black}) + 0.003\ \text{x}\ (\text{age in years})$$

Chronic kidney disease (CKD): Defined as end-stage renal disease managed with chronic hemodialysis or CKD stage 3, 4, or 5 based on a baseline creatinine glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 or clinical documentation. GFR will be estimated from baseline serum creatinine using the 2021 version of the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation.[98]

Chronic cardiovascular disease: Documented history of myocardial infarction or coronary artery disease, congestive heart failure, or peripheral vascular disease.