

Cover Page

Official Title: Esmolol to Control
Adrenergic Storm in Septic Shock - Roll-in

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Consent Form

What	Esmolol to Control Adrenergic Storm in Septic Shock (ECASSS) – ROLL-IN
Where	Intermountain Medical Center
Who	PI: Samuel Brown, MD, MS (801) 507-6556 Co- investigators: Colin Grissom, MD Michael Lanspa, MD, MS Emily Wilson, MS Ithan Peltan, MD Ellie Hirshberg, MD Peter Crossno, MD Vivian Lee, MD Sarah Beesley, MD Samir Parikh, MD Sponsor: Intermountain Medical Center
When	Your participation will last until you are discharged from the hospital.
Why	This research study will evaluate the adequacy and efficiency of study protocols for the main ECASSS study. We are investigating a drug called esmolol as a treatment for serious infection (“septic shock”).
How	While you are receiving infusions of medicines like adrenalin to support your blood pressure, we will infuse a medication called esmolol that we think will help to control the negative effects of the body’s high stress state during serious infection. You will also have some blood drawn and have ultrasound pictures of your heart taken. We will monitor to see how long it takes for your body to improve from the serious infection.

Why is this study being done?

We are asking you to take part in a research study about a drug called esmolol for use in septic shock.

Septic shock is a common condition in which infection interrupts the body's normal system of keeping itself in balance. Septic shock occurs when sepsis, a body-wide inflammatory response to infection, leads to dangerously low blood pressure. One potential way to treat septic shock is to block part of the body's beta-adrenergic system, which is part of the body's stress response. Such a blockade improves blood flow to the heart, decreases the work that the heart has to do, and helps the heart muscle cells. It may also protect blood vessels from harm. Esmolol is a "beta-adrenergic blocker" whose effects can be adjusted from minute to minute.

This research study is a pilot study. Its purpose is to help us to assess the feasibility of conducting a full, complete research study of esmolol infusion in septic shock. This study is being done because there is suggestion that a well-known drug called esmolol can significantly improve outcomes for patients with septic shock.

Throughout this research study, your study doctor will be Dr. Samuel Brown. Dr. Brown and/or his colleagues will communicate with your primary physicians and nurses to coordinate your care.

Why are you asking me to take part in the study?

We are asking you to join because you have been admitted to the ICU with septic shock, and we think that you may be a good candidate for this study.

Approximately 10 people will take part in this study at Intermountain Medical Center.

Please read this form and ask any questions that you may have before agreeing to be in this research study.

Who can be in this study?

You can be in this study if:

- You are 18 years old or older.
- You have septic shock.
- You are receiving vasopressors through a central venous catheter for more than 60 minutes. Vasopressors are medicines that constrict the blood vessels to increase blood pressure.

- You have a heart rate of greater than 90 beats per minutes while receiving vasopressors for more than 60 minutes.
- You meet certain other medical criteria.

Who cannot be in the study?

You cannot participate in this study if:

- You do not give your informed consent.
- You are currently receiving artificial heart support (called “extracorporeal membrane oxygenation”).
- You are pregnant or nursing
- You are on hospice.
- You are a prisoner.
- You have known or current atrial fibrillation (irregular heartbeats).
- You were previously enrolled in this trial.
- You have a known allergy to esmolol.
- You have pulmonary hypertension (high blood pressure in the lungs).
- Your heart is unable to circulate enough blood to supply the organs (called “cardiogenic shock”).
- You have significant atrioventricular dysfunction (a problem with the electrical system of the heart).
- You are receiving clonidine, guanfacine, or moxonidine

Do I have to join?

No, you do not have to join. Your decision to take part in this study is completely voluntary.

What if I decide not to join?

You can choose not to participate in this study. You will still receive standard medical care.

Can I stop being in the study if I change my mind later?

Yes. If you join the study, you can decide to stop at any time.

How do I stop if I do not want to be in the study any longer?

Please tell your study doctor if you are thinking about stopping or if you decide to stop. Your study doctor can tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor if you are thinking about stopping is to discuss what follow-up care and testing could be important to you. Your study doctor can also stop you from taking part in this study any time if he or she believes it is in your best interest to stop or if the study is stopped.

You can ask us to stop collecting your information, though we will still be able to use the information that we have already collected from you. If you would like for us to stop collecting your information, you must inform us in writing. You can give this notice to the Principal Investigator or research team in person or mail it to:

*Samuel Brown, MD
Shock Trauma ICU
Intermountain Medical Center
5121 South Cottonwood Street
Murray, UT 84107*

Once we have received your written request, we will stop collecting your information. You will not be able to continue in the study. You will not be able to join the study again at a later date.

How long will I be in the study?

You will be in the study until you are discharged from the hospital.

What will happen if I decide to take part?

If you are admitted to the ICU with sepsis and you meet the eligibility criteria, we will first ask you to sign this consent form. You will undergo a few assessments before you are given esmolol, the study drug.

Baseline Assessment:

- You will have a full transthoracic echocardiogram (pictures of your heart will be taken with an ultrasound).
- Your blood will be drawn through your IV line.

- We will record your vital signs and related medical information from your medical record.
- We will record your age, sex, and contact information.
- Special EKG leads will be attached near the regular EKG leads to allow us to measure the strength of your heartbeats with a noninvasive device called the “NICOM.”

24-hour Assessment

- You will have a full transthoracic echocardiogram.
- Your blood will be drawn.
- We will record your vital signs and related medical information from your medical record.

Esmolol infusion

We will confirm that you do not have “cardiogenic shock”, and you will be evaluated to see whether you would benefit from salt water infusions, which is a standard treatment for septic shock. Once we have evidence that you won’t benefit from further salt water infusions, you will be given esmolol. This is the only treatment which is experimental and is not done as regular standard-of-care. Esmolol will be increased gradually according to a protocol designed for safety. The esmolol infusion will continue while you are on vasopressors.

Daily on-treatment assessments

Your blood will be drawn while you are receiving vasopressor medications. We will see whether you have any side effects.

Blood samples

Your blood samples will be sent to Beth Israel Deaconess Medical Center (BIDMC), a teaching hospital of Harvard Medical School. BIDMC will perform assays on your blood samples. This is a type of testing that will let us evaluate the state of your blood vessels.

Tissue banking

As part of this study, we would like to preserve your leftover blood samples in a tissue bank to make possible future research. Your blood samples will be kept by Dr. Samir Parikh at BIDMC and will be used to help answer future research questions that may arise. Before your blood samples are sent to BIDMC, they will be de-identified. This means your

sample will be coded so that your name is not on the sample. BIDMC will not receive any information that could be used to identify you. Your samples will be given a number, and the identification code linking your name to the number will be kept by Dr. Brown. If you want to you have your blood sample withdrawn from the sample repository later, please contact Dr. Brown at (801) 507-6556.

Tissue or blood sample obtained from you in this research may help in the development of a commercial product by BIDMC or its research partners. There are no plans to provide financial compensation to you should this occur.

You do not have to participate in the tissue bank to be in the main part of this study. No matter what you decide to do, your decision will not affect your medical care.

You can tell us your choice by initialing one of the choices below:

Yes, my sample(s) may be saved for future research

(initial)

No, my sample(s) must be destroyed at the end of this research project.

(initial)

Hospital discharge assessment

When you are discharged from the hospital, we will determine how many days you have not had shock (out of 14 days), and we will record your discharge destination.

What are the risks to me if I join the study?

The known risks and side effects are listed below. Your study doctor and other study personnel will watch carefully for any side effects, but the doctors do not know in advance all the side effects that can happen. Some side effects are mild and others can be very serious. Some side effects go away when you stop taking the investigational drug but in some cases, side effects can be serious, long lasting or may never go away.

Important: You should talk to your study doctor about any side effects that you notice while you are taking part in the study.

Risks associated with esmolol include:

Cardiogenic shock (if this develops, esmolol will be stopped)

Excessively slow heart rate or low blood pressure (if this develops, esmolol will be

stopped)

Common side effects of esmolol:

Slightly lower blood pressure (esmolol will normally be continued, as this is easily treated)

Infrequent side effects of esmolol include:

Anxiety, Drowsiness, Nausea, Vomiting, Headache, Nervousness, Redness of the face and neck

Rare, but serious side effects of esmolol:

Hypersensitivity (allergic) reaction. This is extremely rare. Patients with known hypersensitivity to esmolol are excluded from the study. Should you have a hypersensitivity reaction, esmolol infusion will be stopped and you will be treated.

Risks and side effects related to the study procedures:

Echocardiogram: This test is non-invasive. There are no risks from this procedure.

NICOM: This is a monitoring system device which is also non-invasive. There are no risks from this procedure.

Blood tests: Only small volumes of blood will be obtained; the risks are minimal, if any.

Risks related to pregnancy

You cannot participate in this study if you are pregnant. You should not breastfeed a baby while in this study.

Are there any benefits to me if I take part in the study?

If esmolol treatment works, we anticipate a direct benefit to patients receiving esmolol infusion, including improved chances of survival and freedom from shock.

Will I be updated about new information or developments?

As the study progresses, the study doctor will talk to you about any new information or developments that may increase your risk. At that time, you can decide whether to continue with the study or not.

What happens if I am injured because I was in the study?

If you become injured while taking part in this study, Intermountain Healthcare can provide medical treatment. We will bill you or your insurance company in the usual way. Because this is a research study, some insurance plans may not pay for your treatment. If you believe you have been injured as a result of being in this study, please call the Principal Investigator right away. You may also call the Office of Research at 1-800-

321-2107.

Who do I ask if I have questions about the study or my rights?

If you have questions about the study, please call the principal investigator, Dr. Samuel Brown, at (801) 507-6556.

If you have questions regarding your rights as a research subject or if problems arise which you do not feel you can discuss with the Investigator, please contact **Intermountain's Office of Research at 1-800-321-2107.**

What are the costs of taking part in the study?

You will not incur any costs related with your participation in this research study. Any procedures that will be performed as your normal standard of care will be billed to you or your insurance company in the usual manner.

Will I be paid if I participate in the study?

You will not be paid for being in this research study.

If I take part in this study, what health information about me will you use?

This is the health information from your medical records that will be used in the study:

- Name
- Address
- Telephone
- Medical history and results of clinical testing and monitoring and evaluation
- Results from tests and procedures to be performed in this study

This health information will come from the information that you give to the researchers and from your medical records at the hospitals and clinics where you've been treated.

The researchers may need to share your information with others; however, this information will not identify you. Information that could identify you will be replaced with a code that will be used instead. The others working on this study who may receive that information are:

- Researchers at University of Chicago and Beth Israel Deaconess Medical Center

Important: You need to know that laws protect your health information when it is held by hospitals and healthcare providers. But if your health information goes to someone else, your health information may not be protected by those laws.

Your health information may be viewed for the following purposes, and laws protect the confidentiality of your health information when used by these groups for these purposes:

- Intermountain's IRB (Institutional Review Board) to oversee the safety and ethics of the study
- Intermountain employees to do their job (such as give treatment, for billing matters or to make sure the research is done correctly).
- The Food and Drug Administration and others to comply with law.

If you decide to take part in this study and sign this form, you permit researchers to use your health information for this study. If you **want** to take part in this study, please **sign** this form. If you **don't** want to participate, please **don't** sign this form.

You can always ask to see your medical information at any time; however, you will not be able to see your health information that is used in this study until the study is finished.

Your agreement—which is called an authorization—to use your health information as part of this study continues without ending.

CONSENT

I have read and I understand this consent document. I have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I understand that sections of any of my medical notes may be looked at by responsible individuals from Intermountain Healthcare or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I will be given a signed copy of the consent and authorization form to keep.

I agree to participate in this research study and I authorize you to use and to disclose health information about me for this study, as you have explained in this document.

Participant's Name (Print)

Participant's Signature

Date & Time

Name of Person Obtaining Authorization and Consent

Signature of Person Obtaining Authorization and Consent

Date & Time

SURROGATE CONSENT

If the participant is unable to give consent and authorization, consent and authorization is given by the following authorized personal representative of the individual.

Therefore, I agree to consent to the treatment of Patient (Name: _____)
and I meet the following conditions of surrogate consent:

Health Care Agent (as named in an Advance Health Care Directive)

Legal Guardian

OR

If no health care agent or legal guardian has been appointed, a Surrogate Health Care Decision Maker is utilized. The health care decision maker must be over 18 years of age; must have health care decision making capacity; must be reasonably available; and has not been disqualified by the patient. The health care decision maker can be in descending order of priority and authority:

Check applicable:

- Spouse; unless divorced, legally separated or found by a court to have acted in a manner that should preclude having a priority position.
- a child.
- a parent.
- a sibling.
- a grandparent.
- a grandchild.
- other; if a family member listed above is not available, this person should exhibit special care and concern for the patient and be familiar with the patient's personal values.
State relationship to patient: _____

Name of Authorized Personal Representative

Signature of Authorized Personal Representative

Date & Time

Name of Person Obtaining Authorization and Consent

Signature of Person Obtaining Authorization and Consent

Date & Time

**INFORMED CONSENT
TO CONTINUE TO
PARTICIPATE IN RESEARCH
and
AUTHORIZATION TO USE & DISCLOSE
PROTECTED HEALTH INFORMATION**

My legal representative previously gave consent for me to be in this research study. This is because I was unable to make my own decision because I was ill.

My condition has now improved. I have read & understand the information on this consent form. All of my questions about the study have been answered to my satisfaction. I freely agree to *continue* to participate in this research study.

I authorize you to use & disclose health information about me for this study, as you have explained in this document.

Participant's Name (Print)

Participant's Signature

Date & Time

Name of Person Obtaining Authorization and Consent

Signature of Person Obtaining Authorization and Consent

Date & Time

Esmolol to Control Adrenergic Storm in Septic Shock (ECASSS) – ROLL-IN

Acronym: ECASSS-ROLL-IN

Version: 5

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1.0 Abbreviations and Definitions

APACHE II = Acute Physiology and Chronic Health Evaluation, version 2
BIDMC = Beth Israel Deaconess Medical Center
CVP = Central venous pressure
ECMO = Extracorporeal Membrane Oxygenation
ER = Emergency Room
GVEC = Graded Volume Expansion Challenge
ICU = Intensive Care Unit
IMC = Intermountain Medical Center
ITT = Intention to Treat
LAR = Legally Authorized Representative
OFFD = Organ-Failure-Free Days at 28 days
P/F = PaO₂/FiO₂ ratio
SAE = Serious Adverse Event
ScvO₂ = Central venous oxygen saturation
SMC = Safety Monitoring Committee
SOFA = Sequential Organ Failure Assessment score
SUSAR = Serious and Unexpected Suspected Adverse Reaction

Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug or study procedure, whether or not considered drug related. (cf. 21 CFR 312.32(a))

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

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

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

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (cf. 21 CFR 312.32(a))

Organ-failure-free days: As of day 28, the number of calendar days on which the patient receives none of (a) vasopressor therapy, (b) mechanical ventilation, or (c) renal replacement therapy. If the patient dies on or before day 28, they have -1 organ-failure-free days.

Serious adverse event (SAE) or serious suspected adverse reaction or serious unexpected suspected adverse event (SUSAR). An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may

require medical or surgical intervention to prevent one of the outcomes listed in this definition. (cf. 21 CFR 312.32(a))

Study Day: The first day of esmolol infusion is study day zero. The next day is study day one, and so on etc.

Study Drug: Esmolol infusion for septic shock patients with persistent tachycardia after adequate volume expansion.

Study hospital: Defined as the hospital where the patient is enrolled.

Study withdrawal: Defined as permanent withdrawal from the study before the completion of study activities. This does not include those subjects who have completed the esmolol infusion. If a patient or surrogate requests to withdraw from the study, investigators should seek explicit permission to continue data collection for relevant outcomes.

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

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure (or package insert) or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. (cf. 21 CFR 312.32(a))

2.0 Study Summary

2.1 **Title:** Esmolol to Control Adrenergic Storm in Septic Shock (ECASSS) – ROLL-IN

2.2 **Objective:** To evaluate the adequacy and efficiency of study protocols for the main ECASSS study.

2.4 **Study design:** Prospective, single arm, feasibility (“roll-in”) study of esmolol infusion in septic shock.

1. **Inclusions.** We will include patients admitted to the ICU for sepsis who are within 48 hours of septic shock and ICU admission and are simultaneously tachycardic (heart rate >90/min) **and** on vasopressors for > 60 min. Patients must meet criteria at the time of enrollment.
2. **Final safety check.** After enrollment and before esmolol infusion, ScvO₂, transthoracic echocardiogram, evaluation of fluid responsiveness, and review of telemetry/EKGs will occur to assure that no exclusion criteria are present.
 - a. If no exclusion criteria are present, patients will start esmolol infusion
 - b. If patient is still fluid responsive but otherwise has no exclusions, fluid will be administered by explicit protocol until no longer fluid responsive, and then the patient will receive esmolol infusion. If tachycardia has resolved as a result of volume expansion, esmolol infusion will not occur until tachycardia and vasopressor administration co-occur. After esmolol infusion, volume expansion will be managed as part of the esmolol titration protocol.
 - c. Patients who fail the final safety check will NOT start esmolol infusion but will be followed for non-interventional aims (e.g., serial TTEs, vascular biomarkers) to understand better the natural history of cardiogenic shock superimposed on septic shock.
3. **Esmolol infusion**
 - a. Esmolol infusion, started without bolus, with slow upward titration to a maximum infusion rate is protocolized (see protocol in Appendix 1), with a target heart rate of 80-90/min.
 - b. Esmolol infusion will be stopped in the event that cardiogenic shock, excessive bradycardia, grade 2 or grade 3 heart block, or hypotension, or bronchospasm occur, as per protocol.
4. **Other care**
 - a. ICU patients are managed according to current Surviving Sepsis campaign guidelines as per usual practice.
 - b. Vasopressor infusion titrations according to protocol are recommended, while clinicians retain the ability to titrate as they feel clinically indicated. Norepinephrine should be the primary vasopressor; at 0.25 mcg/kg/min of norepinephrine, a second vasopressor agent (preferentially, vasopressin 0.03 units/min or epinephrine) may be added; at 0.5 mcg/kg/min, stress-dose steroids (hydrocortisone 150-200 mg IV daily or equivalent, in divided doses) may be added.

2.5 Inclusion criteria

1. Age \geq 18 years
2. Within 48 hours of admission to the ICU and septic shock (sepsis present at time of admission)
 - a. Septic shock defined by consensus criteria as
 - i. At least two SIRS criteria
 - ii. Suspected or documented infection
 - iii. Receiving vasopressors to treat hypotension after at least 20 ml/kg intravenous crystalloid volume expansion
3. Receiving vasopressors through a central venous catheter for more than 60 minutes.
4. Arterial catheter in place or expected to be placed imminently.
5. Heart rate $>$ 90/min while receiving vasopressors for more than 60 minutes.
6. Adequately volume expanded, as manifest by any of the following, performed as part of routine clinical care (i.e., no study procedures will be performed before signed consent). **If none of these measures are clinically available, the clinical attending must confirm that volume expansion is adequate.** (After enrollment, a final safety check will confirm the adequacy of volume expansion.)
 - a. Central venous pressure (CVP) $>$ 15 mm Hg.
 - b. Negative Passive-Leg Raise (PLR) maneuver ($<$ 10% increase in cardiac output after PLR).
 - c. No cardiac output response ($<$ 10% increase) after rapid infusion ($<$ 5 min) of 250 ml of IV crystalloid (i.e., a graded volume expansion challenge [GVEC]).
 - d. For patients who happen to be breathing passively on a positive pressure mechanical ventilator delivering at least 8 ml/kg tidal volumes and in normal sinus rhythm, stroke volume variability $<$ 10% (such patients are acknowledged to be uncommon; *the protocol does not recommend or require the induction of passive breathing*).

2.6 Exclusion criteria

1. Lack of informed consent.
2. Currently receiving ECMO.
3. Known pregnancy or nursing.
4. Patient is a prisoner.
5. Patient on hospice (or equivalent comfort care approach) at or before the time of enrollment.
6. Known or current atrial fibrillation.
7. Previously enrolled in the trial.
8. Known allergy to esmolol or vehicle (see Appendix 2 for BREVIBLOC vehicle ingredients).
9. Receipt of nodal blocking agents (see Appendix 3 for list of such agents) within three half lives
10. Hemoglobin $<$ 7 gm/dl.
11. Cardiac arrest within 24 hours.
12. Pulmonary hypertension (moderate or severe), from documented history of prior right heart catheterization or current evidence on TTE of **any** of the following
 - mPAP \geq 35mmHg

- SPAP \geq 60mmHg
13. Cardiovascular collapse, as manifested by inability to achieve a MAP of 65 mmHg with vasopressor therapy.
 14. Cardiogenic shock, as defined by **any** of the following
 - Cardiac index \leq 2 L/min/m²
 - Ejection fraction \leq 25%
 - ScvO₂ \leq 60%
 - Current infusion of any dose of dobutamine, milrinone, or dopamine
 - Current infusion of epinephrine for clinically diagnosed cardiogenic shock
 15. Significant atrioventricular dysfunction
 - Sick sinus syndrome
 - PR interval > 200 msec
 - Current evidence or prior history of Grade 2 or Grade 3 heart block
 - Pacemaker or plans to place a pacemaker
 16. Pheochromocytoma or status asthmaticus
 17. Receiving clonidine, guanfacine, or moxonidine
 18. Hemoglobin < 7 gm/dl
 19. Cardiovascular collapse (failure to achieve MAP of 65mmHg)
 20. Cardiac arrest within 24 hours
 21. Worse than moderate aortic stenosis
 - Known aortic stenosis, with any of (1) mean gradient \geq 40 mmHg OR (2) maximum gradient \geq 60mmHg OR (3) aortic valve area \leq 1.0cm² OR (4) aortic valve area index \leq 0.85cm²/m² body surface area.
 22. Worse than mild mitral stenosis
 - Known mitral stenosis, with any of (1) valve area \leq 1.5 cm² OR mean gradient \geq 5 mmHg.

2.7 Sample size: The study will enroll up to 10 patients at 1 center.

2.8 Non-clinical outcomes for ROLL-IN:

1. Proportion of eligible patients consented
2. Proportion of compliance with final safety check
 - a. Protocol compliance is considered adequate where compliance is 100% for the safety check.
3. Proportion of protocol compliance
 - a. For the esmolol titration protocol, each hour (the closest value of heart rate to the hour) during the esmolol infusion will be determined to be “in range” or “out of range,” with 3bpm margin for compliance (i.e., heart rate 77 to 93bpm). The initiation and cessation of esmolol will also be included as a timepoint for evaluation of compliance. Protocol compliance is considered adequate where overall compliance on hourly checks is >80%.
 - b. For STOP events, protocol compliance is considered adequate at 100%.
 - i. 30min moving average of cardiac index below threshold
 - ii. 30min moving average of norepinephrine infusion rate above threshold
 - iii. Clinician determines that shock has substantially worsened on esmolol.

- c. For VOLUME EXPANSION events, protocol compliance is considered adequate at 90%.
- 4. Amount of research coordinator time spent on different tasks

2.8.1 Anticipated primary clinical outcome for main trial (this will also be recorded for ROLLIN): Organ-failure-free days at 28 days. An organ-failure-free day is defined as a calendar day on which the patient receives none of (a) vasopressor therapy, (b) mechanical ventilation, or (c) renal replacement therapy.

2.8.2 Anticipated secondary clinical outcomes for main trial (these will also be recorded for ROLLIN):

1. All-cause hospital mortality
2. All-cause 28-day and 90-day mortality
 - a. Mortality will be ascertained through telephone followup for patients who were discharged alive before 90 days.
3. Peak serum high-sensitivity troponin
 - a. Troponin will be measured on day 0 and day 1.
4. LV global longitudinal strain at 24 hours
5. Time to transition to quiescent vascular phenotype, as defined by serum Angpt-2 level < 1ng/ml.
6. ICU-free days to day 28
 - a. Patients who die before 28 days will be assigned -1 ICU-free days, using a methodology similar to that used for organ-failure-free days.
7. Cardiogenic shock/requirement for inotropes through day 14. This is a binary variable and is met when any of the following is present
 - a. Dobutamine or milrinone infusion at any dose, lasting > 60min
 - b. $CI \leq 2$ L/min/m² lasting > 30 min on NICOM
 - c. $ScvO_2 \leq 60\%$ on any measurement
8. Development of second or third degree heart block.

3.0 STUDY DESCRIPTION

3.1 Background

3.1.1 Septic shock is a significant clinical and scientific problem

Septic shock, a common syndrome in which infection leads to potentially fatal disruption of organismal homeostasis, accounts for 10% of all ICU admissions and 30% of all ICU mortality. Approximately 200,000 patients die annually in the USA from septic shock. Septic shock is a state of extreme biological stress associated with rapidly evolving hemodynamic, physiologic and metabolic dysfunction, as the host attempts to reestablish homeostasis in the face of severe infection.^{1,2} Progressive cardiovascular dysfunction is often the penultimate step before death from septic shock.³

3.1.2 Sympathetic nervous system over-stimulation impairs cardiovascular function in septic shock

While immune activation and autonomic nervous system stimulation are crucial to the adaptive host response to infection, in the right setting (high pathogen virulence or infectious load, genetics of the host, non-genetic susceptibility, duration of time without anti-infective therapy) these adaptive responses become pathogenic. Sympathetic over-

stimulation can drive a positive feedback loop of cardiovascular and other organ dysfunction, the “multiple organ dysfunction syndrome” (MODS), which is the signature of septic shock. The hemodynamic changes of septic shock result from dynamic interactions between cardiovascular system homeostasis, the host immune response, and therapeutic interventions such as catecholamine infusions and intravascular volume expansion.¹ Ironically, although endogenous catecholamines—which engage the widely distributed α - and β -adrenergic receptors—are increased ~20-fold in septic shock, administration of exogenous catecholamines is a cornerstone of current management.⁴ The adrenergic over-stimulation in septic shock is of central interest because (1) cardiovascular dysfunction is central to the MODS that precedes death, (2) the usual treatment paradigm for septic shock involves further adrenergic stimulation, (3) there are safe, effective, and selective adrenergic antagonists that may be beneficial in treatment of septic shock, and (4) there are now non-invasive methods to assess cardiovascular responses to septic shock and its treatment. An integrative approach to the interplay between the sympathetic nervous system and cardiovascular dysfunction in sepsis may be crucial to improving outcomes after septic shock. This harmful interplay affects both elements of the cardiovascular system: the heart and the blood vessels.

3.1.3 Adrenergic over-stimulation harms the heart

The hyper-adrenergic state, in combination with excess cytokine production, results in a spectrum of myocardial injury often grouped under the general category of septic cardiomyopathy. Septic cardiomyopathy is remarkably common, despite a historical belief that sepsis was primarily or exclusively a hyperdynamic state.^{5,6} Abnormalities of systolic¹ and diastolic^{7,8} function are independent risk factors for death from septic shock.³ Autopsy studies of septic shock demonstrate extensive myocyte injury, contraction band necrosis, and interstitial edema in 90-100% of patients.^{9,10} The catecholamine therapy used to treat septic shock may, paradoxically, worsen septic cardiomyopathy. Indeed, the extent of myocardial necrosis has been shown to correlate with dose and duration of catecholamine therapy.⁹ Recent observational studies show that catecholamine inotrope use is associated with an increased 90-day mortality in septic shock after adjusting for disease severity and propensity to receive catecholamine inotropes.⁶ Catecholamine over-stimulation can incite a parallel syndrome called “tako tsubo” or “catecholamine” cardiomyopathy in non-septic individuals. Tako tsubo cardiomyopathy shares functional, pathological, and clinical features with septic cardiomyopathy, and is also associated with increased mortality.¹¹ Though distinct from septic cardiomyopathy, tako tsubo cardiomyopathy provides independent evidence of catecholamine cardiotoxicity.

3.1.4 Adrenergic over-stimulation harms the vasculature

The cellular basis for inflammation-induced vascular permeability is well described.¹²⁻¹⁵ Junctions between adjacent endothelial cells rapidly disassemble in response to inflammatory triggers, resulting in vascular leakage. Vascular leakage not only contributes to shock, and lung injury, but inflamed endothelium posts an array of cell surface molecules that promote leukocyte adhesion and thus end organ damage.^{12-14,16} Observational studies suggest that sympathetic over-stimulation is linked to endothelial cell damage.¹⁷⁻¹⁹ Given (A) the vasculature’s emerging importance in septic shock outcomes, (B) the paucity of knowledge regarding catecholamine action on the endothelium, and (C) multiple reports that even non-septic states of adrenergic excess induce vascular inflammation and injury,²⁰⁻²³ there is a pressing need to understand how β -blockade may ameliorate the pro-leakage, pro-inflammatory vascular phenotype of septic shock.

3.1.5 The heart and blood vessels represent an integrated system

The primary expression and determinant of mortality in septic shock is the integrated host cardiac and vascular response to infection and inflammation. Inflammatory cytokine release is associated with myocardial depression, endothelial barrier dysfunction, and vascular hyporeactivity. Together, these responses lead to the classic “distributive” physiology of septic shock, compounded by increasingly recognized myocardial dysfunction. The cardiovascular system is controlled by an ancient neural-endocrine system that regulates the integrated function of heart and vessels. Via this baroreflex system, the autonomic nervous system regulates systemic perfusion by adjusting vascular tone, compliance, cardiac contractility, and heart rate. While traditionally heart and vasculature are considered separately, in reality they are an integrated system. Microvascular dysfunction within the heart results in myocardial edema, whereas extracardiac microvascular dysfunction contributes to MODS. Thus microvascular dysfunction affects both intracardiac and extracardiac vessels, contributing to septic cardiomyopathy and MODS, playing a crucial role in the pathological positive feedback loops that characterize septic shock. Furthermore, cardiac dysfunction contributes to downstream endothelial dysfunction.

Heart rate variability, a non-invasive measure of the baroreflex measured from changes in the inter-beat interval, allows for the inspection of integrated cardiovascular function. Heart rate variability provides unique insights into severity of illness in primary cardiac disease,²⁴⁻²⁶ acute trauma²⁷ and sepsis.^{28,29} In healthy states, heart rate exhibits nonlinear patterns of complexity, including fractal self-similarity across time scales.^{30,31} A technique called detrended fluctuation analysis, which quantifies the variability in inter-beat intervals over different time scales, allows the assessment of whether fractal complexity is preserved or disrupted. Fractal complexity was strongly associated with early outcomes in septic patients in research conducted by this research team³² and was associated with sepsis in neonates, a population for which heart rate variability has been extensively evaluated.³³

3.1.6. β -adrenergic blockade may be therapeutic in septic shock

Norepinephrine, the primary adrenergic agonist maintaining vasomotor tone in septic shock, commonly increases heart rate and myocardial contractility, but excessive stimulation results in cell death followed by fibrosis and pathological remodeling, effects predominantly mediated via β -adrenergic receptors. Excess catecholamines also have a direct cardiotoxic effect through oxidative damage on the myocardial membrane.³⁴ β -blockers have long demonstrated utility in non-septic myocardial dysfunction through mechanisms, including (a) inhibition of direct cardiotoxic effects of catecholamines, (b) improvement in myocardial function by reducing heart rate and oxygen demand, (c) attenuation of neurohormonal vasoconstriction and apoptotic mechanisms, and (d) protection of the microvasculature.³⁵

While advocacy for β -blockade in sepsis has recently risen, little is understood about *in vivo* mechanisms of effect during the adrenergic storm of sepsis.³⁶⁻³⁹ A pilot randomized, unblinded trial of esmolol infusion in tachycardic patients with septic shock suggested that this β 1-blocker was associated with significantly decreased mortality, higher stroke volume, lower arterial lactate, and lower norepinephrine dosage.^{40,41} Unfortunately, the control-group hospital mortality was 81%, far higher than predicted by current severity scores, thus limiting generalizability. That trial also failed to provide important mechanistic insights. Nonetheless, the positive overall result from the Italian phase 2 trial identifies both the safety of esmolol infusions in septic shock patients with tachycardia

and suggests an urgent need to conduct a more definitive and mechanistically sophisticated clinical trial.

3.1.6.1. β -adrenergic blockade has direct cardiac effects

In the heart, β -blockade improves coronary perfusion, decreases myocardial work, and directly reduces cardiomyocyte dysfunction, especially via selective β 1-blockade. The net effects can be monitored via measurement of left ventricular (LV) strain,⁴²⁻⁴⁶ a technique our group has repeatedly validated as a more sensitive and specific marker of cardiac dysfunction in septic patients. Additionally β 1-blockade may improve myocardial performance (especially through providing more time for ejection and relaxation, as measured by the tissue Myocardial Performance Index). β -blockade has long been considered an option for improving autonomic nervous system homeostasis and restoration of heart rate variability: after myocardial infarction β -blocker improves parasympathetic tone.⁴⁷

3.1.6.2. β -adrenergic blockade has effects on the microvasculature

To prevent unopposed vascular leakage and inflammation, the endothelium possesses natural braking mechanisms. The Tie2 pathway appears to be a central actor in the braking response. Tie2 is a receptor expressed predominantly by endothelial cells, where it maintains vascular barrier function.^{48,49} Normally, Tie2 is tonically activated by Angiopoietin-1 (Angpt-1), a protein ligand secreted from nearby vascular smooth muscle cells. As our group and others have shown, activated Tie2 both maintains barrier function and defends the barrier against virtually all known triggers of permeability—indeed, in the context of experimental sepsis, Tie2 activation by Angpt-1 improves organ function and survival.⁵⁰⁻⁵⁷ During inflammatory states, the function of Tie2 is antagonized by a ligand secreted from the endothelium itself called Angpt-2. Angpt-2 unseats Angpt-1 from the receptor, deactivates signaling through Tie2, and as a result, potentiates inflammation and vascular leakage. Circulating Angiopoietin levels predict vascular injury and adverse outcomes in sepsis and other critical illness,⁵⁸ while therapeutic inhibition of Angpt-2 rescues vascular leak and mortality in experimental sepsis.⁵⁹⁻⁶¹ In sum, Tie2 appears to be a major toggle for the endothelium to switch between barrier protection and vascular leakage.⁵³⁻⁵⁷

Several lines of evidence suggest that β -blockade may improve endothelial function, especially via Tie2. A pilot study of infantile hemangioma suggested a potent regressive effect of β -blockade on these benign endothelial tumors;⁶² a follow-up controlled trial demonstrated ~15-fold improvement with β -blockade.⁶³ Crucially, these inherited hemangiomatous disorders arise from mutations in *TIE2*.^{64,65} Specific to sepsis, an uncontrolled study in humans⁴⁰ and a randomized trial in rats⁶⁶ suggested that esmolol infusion significantly improved endothelial function and in turn, overall survival.

3.2 Study Design

Prospective, single arm, feasibility (“ROLL-IN”) study of esmolol infusion in septic shock.

3.3 Objective

To assess the adequacy of subject identification and enrollment procedures. To assess the adequacy and efficiency of study protocols. To evaluate the estimates of coordinator burden for screening and enrollment.

3.5.1 Non-clinical outcomes for ROLL-IN:

1. Proportion of eligible patients consented
2. Proportion of protocol compliance
3. Amount of research coordinator time spent on different tasks

3.5.2 Anticipated primary clinical outcome for main trial: Organ-failure-free days at 28 days. Defined as the number of calendar days on which the patient receives none of (a) vasopressor therapy, (b) mechanical ventilation, or (c) renal replacement therapy. (Patients who die before 28 days will be assigned -1 organ-failure-free days in order to avoid making death equivalent to prolonged organ dysfunction.) For example, a patient who died on day 12 would have -1 organ-failure-free days, while a patient who resolved all organ dysfunction on day 9 but died on day 30 would be categorized as having 19 organ-failure-free days.

3.5.3 Anticipated secondary outcomes for main trial

1. All-cause hospital mortality
2. All-cause 28-day and 90-day mortality
 - a. Mortality will be ascertained through telephone followup for patients who were discharged alive before 90 days.
3. Peak serum high-sensitivity troponin
 - a. Troponin will be measured on day 0 and day 1.
4. 24-hour LV strain, as assessed by echocardiography
5. Days to transition to a quiescent vascular phenotype.
6. ICU-free days to day 28
 - a. Patients who die before 28 days will be assigned -1 ICU-free days, using a methodology similar to that used for organ-failure-free days.
7. Cardiogenic shock/requirement for inotropes through day 14. This is a binary variable and is met when any of the following is met
 - a. Dobutamine or milrinone infusion at any dose, lasting > 60 min
 - b. $CI \leq 2$ L/min/m² lasting > 30 min on NICOM
 - c. $ScvO_2 \leq 60\%$ on any measurement

3.6.2 Anticipated prespecified subgroups

1. Patients with abnormal LV strain on the initial echocardiogram (>-18%)
2. Patients with an abnormal tMPI (> 0.39) on the initial echocardiogram
3. Patients receiving an epinephrine infusion at the time of enrollment
4. Patients with a non-quiescent vascular phenotype at the time of enrollment
5. Patients over the age of 65 years

4.0 Study population and enrollment

The study will enroll 10 patients at one clinical center. Patients will be recruited from the ICUs of Intermountain Medical Center. The objective is to screen every newly admitted patient with septic shock to determine eligibility.

4.1 Screening

Appropriate subjects will be identified through review of the ER census and Intensive Care Unit (ICU) log several times a day, or by automated computer alerting, where available. Patients who are admitted from the ER of an outside hospital will be considered; patients transferred from an inpatient ward/ICU at an outside hospital will not be considered. Patients who are transferred to the ICU from a hospital ward of the study hospital will be considered if (a) sepsis was present at the time of admission to the hospital ward from the study hospital ER, and (b) the total time on the hospital ward was less than 24 hours. Permission to approach patients and/or their families will be requested from the clinical team caring for the patient. All patients meeting inclusion criteria will be entered into a screening log. Intermountain Medical Center has dedicated study physicians and coordinators who are certified and trained in human subjects protection and understand the study protocol. These individuals will oversee and/or perform screening and enrollment activities.

4.2 Inclusion Criteria

Subjects will be considered eligible for the study when they are older than 18 years of age, admitted to an ICU with septic shock, and for at least an hour, they are receiving vasopressors through a central venous catheter and have a heart rate > 90/min. Subjects must meet the heart rate and vasopressor criteria at the time of enrollment.

Inclusion Criterion	Justification/Description
Age ≥ 18 years	Children are physiologically distinct from adults
Septic shock	Meets consensus criteria: <ol style="list-style-type: none"> ≥2 SIRS criteria Suspected or confirmed infection Receiving vasopressor infusion to treat hypotension after at least 20ml/kg intravenous crystalloid volume expansion
Adequately volume expanded	Designed to include only non-compensatory tachycardia, that which persists after adequate volume expansion. Being no longer fluid responsive requires any one of <ol style="list-style-type: none"> CVP > 15 mmHg Negative Passive Leg Raise (PLR) maneuver (< 10% increase in cardiac output during PLR) Stroke volume increase < 10% in response to rapid (< 5 min) infusion of at least 250 ml crystalloid solution In patients being passively mechanically ventilated, stroke volume variability (measured by a valid method, including NICOM) < 10%
Receiving vasopressor infusion via central venous catheter	At least 60 min of any infusion rate of norepinephrine, epinephrine, vasopressin, or phenylephrine
Current or imminent placement of arterial catheter	Allows continuous measurement of blood pressures during esmolol infusion and is standard in the study ICU.
Tachycardia (>90/min)	Heart rate must remain > 90/min for at least one hour, <i>while</i> the patient is receiving vasopressors

4.3 Exclusion Criteria

Exclusions are designed to protect patient safety and maximize scientific integrity. They primarily relate to individuals who may not tolerate β -blockade. Coenrollment in other interventional studies will not be allowed.

4.3.1 List of Exclusions and Reason for Exclusions

Exclusion Criterion	Justification/Description
Cardiogenic shock	Safety consideration: β -blockade may worsen preexisting cardiogenic shock. Cardiogenic shock defined as <i>any one of</i> <ol style="list-style-type: none"> Cardiac Index ≤ 2 L/min/m² ScvO₂ $\leq 60\%$ Ejection Fraction $\leq 25\%$ Current infusion of any dose of dobutamine, milrinone, or dopamine Current infusion of epinephrine to treat clinically diagnosed cardiogenic shock.
Preexisting heart block	Safety consideration: β -blockade may worsen heart block. Defined as any of the following <ol style="list-style-type: none"> Sick sinus syndrome PR interval > 200 msec Any current evidence or history of Grade 2 or Grade 3 heart block Pacemaker or plans to place a pacemaker
Atrial fibrillation at time of enrollment	Substantial noise associated with exposure, hemodynamic measurements, and outcomes; may require independent heart rate control or cardioversion.
Current nodal blockers or anti-arrhythmic agents	Safety consideration: risk of excess nodal blockade. Increased experimental noise. Receipt of any of the following within 3 half lives (see full list in Appendix) <ol style="list-style-type: none"> Non-dihydropyridine calcium channel blockers Digitalis Anti-arrhythmics (e.g., amiodarone, dronedarone, mexiletine) Beta blockers
Receiving clonidine, guanfacine, or moxonidine	Safety issue
Moderate or severe pulmonary hypertension	Possible safety consideration; risk of hemodynamic deterioration. Defined as a documented history of prior right heart catheterization or current evidence on TTE of any of the following. <ol style="list-style-type: none"> mPAP ≥ 35 mmHg SPAP ≥ 60 mmHg
Allergy to esmolol or vehicle	Rare, but required for patient safety.
Admitted for hospice or comfort care	Incomplete and biased data on both exposure and outcome.
Inability to obtain consent within 48 hours of ICU admission	This study does not qualify for waiver of consent
Active pregnancy or nursing	Physiology of pregnant patients distinct; potential risks to fetus unknown; drug levels in breast milk.
Prisoners	Septic shock is not specific to prisoners, so ethical concerns emphasize the protection of autonomy.
Previously enrolled in this trial	Violation of the independence assumption.
Pheochromocytoma or status asthmaticus	Safety issue associated with beta blockade
Hemoglobin < 7 gm/dl	Exclude anemia as cause of tachycardia; avoid risk of impaired oxygen delivery related to anemia
Cardiovascular collapse	Safety consideration; failure to achieve 65mmHg MAP with vasopressors.

Cardiac arrest within 24 hours	Safety consideration
Worse than moderate aortic stenosis	Known aortic stenosis, with any of (1) mean gradient ≥ 40 mmHg OR (2) maximum gradient ≥ 60 mmHg OR (3) aortic valve area ≤ 1.0 cm ² OR (4) aortic valve area index ≤ 0.85 cm ² /m ² body surface area. This is a hypothetical safety consideration.
Worse than mild mitral stenosis	Known mitral stenosis, with any of (1) valve area ≤ 1.5 cm ² OR mean gradient ≥ 5 mmHg. This is a hypothetical safety consideration.

4.4 Enrollment Time Window

Patients must be enrolled within 48 hours of ICU admission and septic shock and must still meet inclusion criteria at the time of enrollment.

4.5 Women and Minorities

Every effort will be made to assure adequate representation of women and minorities. The study inclusion and exclusion criteria (other than the pregnancy exclusion) do not differentially exclude women or minorities.

5.0 Study Procedures

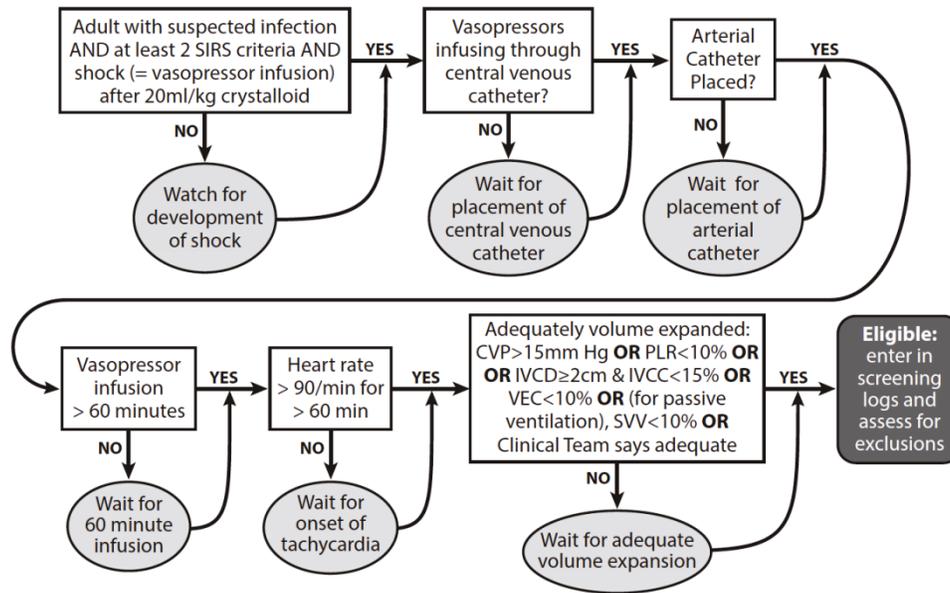
5.1 Common Management Strategies

5.1.1 Study Startup Procedures

Potential candidates will be screened according to the algorithm outlined in FIGURE 1. A study investigator will review, with the research coordinator, all study inclusions and exclusions before consent and enrollment.

Figure 1

EVALUATING INCLUSION CRITERIA



5.1.1.1 Review for final exclusions

A study investigator will review, with the research coordinator, all study inclusions and exclusions before consent and enrollment. After enrollment, according to the protocol depicted in FIGURE 2, study personnel will confirm that cardiogenic shock is absent and adequate volume expansion has occurred. These evaluations are performed after consent because they involve study procedures, which cannot be required of subjects who have not consented. If cardiogenic shock is documented at this point, a subject will be followed for outcomes and biomarkers but esmolol will *not* be infused. After the final safety check has been completed and the patient is confirmed eligible for study drug infusion, study drug infusion should be started as soon as possible and within 3 hours of passing the final safety check.

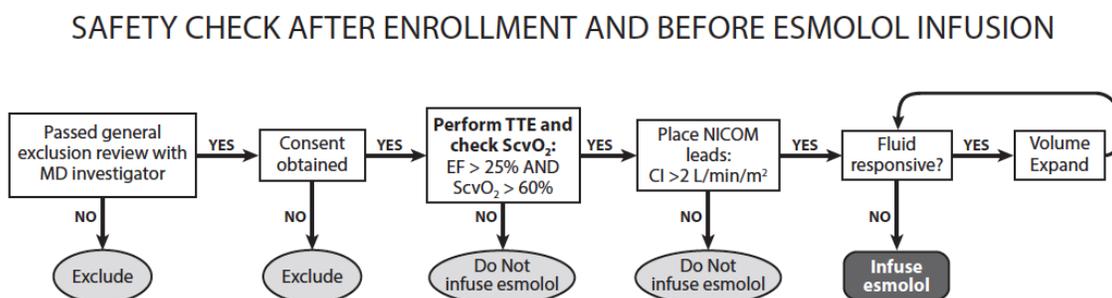
5.1.1.2 Evaluation for cardiogenic shock

If cardiogenic shock is documented at this point, a subject will be followed for outcomes and biomarkers but esmolol will not be administered. This step involves evaluation of LV ejection fraction, measurement of ScvO₂, and direct measurement of cardiac index using the NICOM bioreactance device.

5.1.1.3 Review of fluid responsiveness/adequacy of volume expansion

After the lack of cardiogenic shock has been confirmed and still before esmolol infusion, subjects will be evaluated for fluid responsiveness. Once the subject has been determined to no longer be fluid responsive, applying the tests outlined in section 4.2, esmolol will be infused. If, in the investigator's best judgment, one of those markers of fluid responsiveness is providing a false negative result, s/he may require additional volume expansion, in consultation with the treating team, before initiation of esmolol infusion.

Figure 2



5.1.2 Ventilator management

ARDS Network low-stretch ventilation (as is the standard at IMC) will be used for all mechanically ventilated patients, given the proportion of patients with septic shock who have ARDS and evolving data suggesting that patients at risk for ARDS merit low-stretch ventilation. Ventilator weaning will be performed as per institutional protocol. Weaning will not wait until esmolol infusion has ceased.

5.1.3 Baseline Assessment

In addition to the evaluation for inclusion and exclusion criteria, the following parameters will be obtained on all subjects. Unless otherwise specified, measurements will be those closest in time to enrollment.

- Full TTE, including strain measurements
- Serum for troponin
- Plasma for vascular biomarkers (e.g., angiotensin)
- Heart rate variability
- Vasoactive medications (e.g., agent, infusion rate)
- Vital signs
- Ventilator settings (e.g., PEEP, PF or SF ratio, tidal volume, plateau pressure)
- Admission APACHE II/IV score and components
- SOFA scores and constituents
- Age
- Sex
- Race/ethnicity
- Contact information

5.1.4 24-hour assessment, including early protocol

- Full TTE, including for strain
- Serum for vascular biomarkers, including Troponin
- Heart rate variability
- Vasoactive medications (e.g., agent, infusion rate)
- SOFA scores and constituents
- APACHE II/IV score and constituents
- Vital signs
- Ventilator settings (e.g., PEEP, PF or SF ratio, tidal volume, plateau pressure)

5.1.5 On-treatment assessments

- Incidence of protocol violations
- Incidence of adverse reactions
- SOFA scores and constituents
- APACHE II/IV score and constituents

5.1.6 Hospital discharge assessment

- Organ-failure-free days at 28 days
- Vital status at hospital discharge
- Discharge destination (home, home with services, SNF, rehab, LTACH)

5.1.7 Management of blood samples

- Troponin will be tested in the Intermountain clinical laboratory
- Vascular biomarkers will be tested in Dr. Parikh's laboratory at BIDMC. Locally at IMC, they will be centrifuged and stored at -80C before transportation on dry ice.

5.2 Esmolol infusion

The esmolol infusion will be managed as per the protocol in APPENDIX 1. Esmolol will be stopped and cannot be restarted without explicit investigator approval for STOP events. Further needs for volume expansion will be assessed on the basis of VOLUME EXPANSION events. If the patient is taken to the operating room, esmolol

infusion will be stopped when the patient leaves the ICU for the OR and will only be resumed after reevaluation of cardiac index and adequacy of volume expansion, given the possibility of changes in volume status and degree of shock during surgery.

6.0 Data Collection and Safety Monitoring

6.1 Data Collection and Data Quality Monitoring

Research coordinators and/or investigators will collect data and record them on paper or electronic CRFs. Data will be analyzed internally. Data quality will be reviewed using front-end range and logic checks at the time of data entry and back-end monitoring of data. Patient records and case report forms will be examined on a random spot check basis to evaluate the accuracy of the data entered into the database and monitor for protocol compliance.

6.2 Safety Monitoring

The safety of this feasibility “roll-in” study will be monitored by a three-member safety monitoring committee (SMC). The SMC will have full access to all study data (including a narrative account of each patient’s course) and will review for any major adverse events at 3 patients enrolled and at 6 patients enrolled. While septic shock is a high-mortality condition at baseline, every death during esmolol infusion will be reported (including narrative account and full study data) within 24 hours to the chair of the SMC by the study PI. Further details of safety monitoring and reporting are given at Appendix 4.

7.0 Statistical plan

7.1 Statistical Analysis

The primary comparison is between treatment assignment and organ-failure-free days at 28 days. Secondary analyses are the evaluation of adequacy of screening, enrollment, and study protocols.

7.2 Sample size

This “roll-in” feasibility study will allow us to confirm the adequacy of compliance with management protocols, and the time intensity of study enrollment and CRF completion. These roll-in data will be used to allow rapid initiation of a much larger multi-center trial once funding is secured.

7.3 Additional data

Investigators at the University of Chicago are performing a parallel study under similar protocol, overseen by the University of Chicago IRB and monitored by their own Safety Monitoring Committee. Data from the University of Chicago study will be shared with investigators at IMC to allow analysis of the experience at the two centers. All data transfers will be over-seen by applicable IRB approvals, consent documents, and data use/data sharing agreements and will not occur without appropriate agreements and

approvals in place. Data privacy and confidentiality for the University of Chicago data will comply with relevant regulations and safeguards.

8.0 Risk Assessment

8.1 Potential Risks

There are potential risks (as well as benefits) to study subjects. Selective β 1-blockade in septic shock has reasonable pilot data in favor of its safety; our observations about improved survival with relative bradycardia also suggest that interventions to induce relative bradycardia will be safe. The primary concerns about risk related to β 1-blockade in septic shock (based on theoretical considerations) are of decreased cardiac output, which is why we will titrate esmolol without bolus doses, starting at very low doses, and we will exclude patients with preexisting or intercurrent cardiogenic shock. After enrollment and before esmolol infusion, we will perform a final verification that cardiogenic shock is not present (using the NICOM™ measurements and initial research echocardiogram). Patients with preexisting conduction system disease may also be at risk for heart block or excessive bradycardia, so they are excluded from this study as well (this will also be verified before esmolol infusion, from the EKG monitors at the patient's bedside).

We have chosen esmolol because it is β 1-selective (thereby decreasing the hypothetical risk of pulmonary effects possible with non-selective β -blockade), because it is available as a continuous infusion (thereby limiting the risk of bolus-associated adverse effects) and because it has a very short half-life (allowing essentially immediate cessation of effect when the infusion is stopped). The theoretical side effects of esmolol infusion would all reverse within minutes of discontinuation of esmolol, and explicit rules will dictate discontinuation of esmolol infusion.

8.1.1 Alternative treatments

While some individual clinicians have advocated use of intravenous metoprolol, another β 1-blocker, the longer duration of action and the lack of availability as a continuous infusion led us not to recommend metoprolol for this trial. There is no evidence-based alternative treatment currently available for the adrenergic over-stimulation associated with septic shock. Since participation in this study is voluntary, all patients who choose not to enroll will receive the treatment consistent with the highest standard of care established at their institutions.

8.2 Risk abatement strategies

8.2.1 Cardiogenic shock. As indicated above, patients with preexisting cardiogenic shock are excluded from enrollment, and after enrollment a formal evaluation to exclude cardiogenic shock will be performed before esmolol infusion. The esmolol titration protocol incorporates continuous monitoring of cardiac output using the non-invasive NICOM™ device, and in the rare situation that cardiogenic shock should ensue, esmolol titration will be discontinued and appropriate supportive measures will be instituted. Our use of a no-bolus, slow upward titration protocol for the esmolol infusion is specifically designed to avoid this potential complication.

8.2.2 Excessive bradycardia and/or hypotension. As indicated above, patients with preexisting conduction system disease are excluded from enrollment, and a formal evaluation to exclude conduction system disease will be performed before esmolol infusion. In the event that hypotension or excessive bradycardia should ensue during esmolol infusion, esmolol will be discontinued and appropriate supportive measures will

be instituted. Our use of a no-bolus, slow upward titration protocol for the esmolol infusion is specifically designed to avoid this potential complication.

8.2.3 Hypersensitivity reaction. This is extremely rare. Patients with known hypersensitivity to esmolol or vehicle are excluded from the study. Should this occur, esmolol infusion will be stopped and appropriate treatment measures will be instituted. The short half-life of esmolol avoids concerns about treatment of anaphylaxis in patients on β -blockers, should anaphylaxis occur.

8.3 Protection against loss of privacy/breach of confidentiality

In order to protect a potential subject's privacy, study staff will only approach potential subjects (or LARs) in a private setting. Once consented, we will take multiple steps to protect the study subject from breach of confidentiality. The list linking the subject's name and medical record number will be kept behind the hospital firewall in a password-protected file. This file is only accessible through the hospital server to those individuals given password approval to access the file. Furthermore, the electronic database (REDCap) will be coded with a unique study identifier rather than with individually identifiable PHI (other than certain dates of service, as indicated above). The paper copy of CRFs will be stored in a locked cabinet at Intermountain Medical Center. The plasma sent to BIDMC for vascular biomarker assays will be managed according to standard practice for research samples, under an appropriately executed material transfer agreement.

8.4 Potential benefits

If esmolol proves efficacious, we anticipate a direct benefit to patients receiving esmolol infusion, specifically improvements in organ-failure-free days and/or survival.

8.5 Risks vs. benefits

We have specifically designed the study intervention and esmolol titration protocol to minimize to the maximal extent possible the risks associated with this study. Based on our preliminary data and an Italian pilot study, we believe that the risk-to-benefit ratio for individual patients is favorable.

9.0 Human Subjects

Each study participant or a legally authorized representative (LAR) must sign and date an informed consent form. Institutional review board (IRB) approval is required before any subject is entered into the study.

9.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require equity/distributive justice in human subjects research. The participating ICUs will be screened to determine whether any patient meets inclusion and not exclusion criteria, drawing on routine clinical data. No protocol-specific tests nor procedures will be performed as part of the screening process. Potential subjects will not be approached until the clinical team has granted oral permission to approach the patient and/or LAR for informed consent. Study exclusion

criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. The recruitment of subjects are therefore equitable/just.

9.2 Justification for Including Vulnerable Subjects

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

9.3 Informed Consent

Federal regulations at 45 CFR 46.111(a)(5) require informed consent to participate in research. As ECASSS will enroll critically ill, intubated patients, the large majority of initial consents will be from the subject's LAR, and thus the remainder of this section will focus on LARs. The investigator is responsible for ensuring that the LAR understands the risks and benefits of participating in the study, and answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the LAR's willingness to continue the subject's participation in the trial. The consentor will make every effort to minimize coercion, including not allowing a Study Investigator to participate in obtaining consent when s/he is currently providing clinical care to the subject. All study participants or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the LAR in simple terms before the subject is entered into the study, and to document that the LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The Study Investigator is responsible for ensuring that informed consent is obtained from each subject or LAR. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study agent.

9.4 Continuing Consent

For subjects for whom consent was initially obtained from a LAR, but who subsequently regain decisional capacity while in hospital, investigators will seek formal re-consent for continuing participation, inclusive of continuance of data acquisition. The initial consent form signed by the LAR will reflect that such consent will be attempted and will be updated when such "re-consent" is obtained.

9.5 Withdrawal of Consent

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

patient or LAR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

9.6 Identification of LARs

Many of the patients approached for participation in this research protocol will be decisionally impaired due to their critical illness. Hence, most patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the participants legally authorized representative (LAR), as defined at 45 CFR 46 102 (c). In this study, LARs will be identified as stipulated by relevant regulations and statutes as required by IRBs, as per the standards defined for clinical decision making, as is the standard practice in human subjects research.

9.7 Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires when appropriate, adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all case report forms and reports will be identified only by a coded number. The coded number will be generated by a computer, and only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained inside a locked office.

10 Adverse Events

Patient safety is central to this study protocol. Each investigator is responsible for the safety of the study participants under his/her care. Investigators will determine daily whether any adverse events occurred during the period from enrollment through 24 hours after the completion of the esmolol infusion.

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

- Serious adverse events
- Nonserious adverse events that are considered by the investigator to be related to study drug or study procedures or of uncertain relationship (Appendix 4)
- Adverse events that lead to permanent discontinuation of the study drug infusion. STOP events, as outlined in the titration protocol, are reported separately, recognizing that STOP events often will be related to the underlying septic shock rather than being drug- or protocol-related, as determined by their persistence for more than 20min after discontinuation of esmolol (at which points the effects of esmolol will have resolved). STOP events that require the permanent discontinuation of study drug infusion will be reported as adverse events.

A clinical trial adverse event is any untoward medical event associated with the use of a drug or study procedure in humans, whether or not it is considered related to a drug or study procedure.

After randomization, adverse events related to protocol procedures or occurring after the patient receives the first dose of study drug must be evaluated by the study investigator. If the adverse event is judged to be reportable, the investigator will report to

the SMC his/her assessment of the potential relatedness of each adverse event to study drug or study procedure. Investigators will assess if there is a reasonable possibility that the study drug or procedure caused the event, based on the criteria outlined in Appendix 4. Investigators will also consider whether the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant therapies.

10.2 SERIOUS ADVERSE EVENTS

Serious adverse event collection begins after the patient or LAR has signed informed consent and has received study drug or undergone study procedures. If a patient experiences a serious adverse event after consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a study procedure.

Investigators must alert the chair of the SMC of any **serious and study drug or study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix 4 for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs).

As per federal definitions (primarily in 21 CFR 312.32(a)), a **serious** adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening event, one that places the subject at immediate risk of death (this does not include an event that, had it been more serious, would have placed the subject at immediate risk of death)
- Prolonged inpatient hospitalization or rehospitalization
- Persistent or significant disability/incapacity, indicating a substantial disruption of a person's ability to conduct normal life functions (i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life).

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

Given the short-acting nature of esmolol and the limited duration of the study infusion, surveillance for adverse events will extend through 24 hours after completion of the esmolol infusion. Serious adverse events will be collected during and for 24 hours after the esmolol infusion, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to study drug or a protocol procedure.

APPENDIX 1

ECASSS ROLL-IN Study Drug Titration protocol

Fundamental rules for study drug titration:

The target heart rate is 85 bpm. Start study drug infusion at 20 mcg/kg/min, without bolus, if HR \geq 100 bpm. If HR >90 bpm and <100 bpm, start study drug infusion at 10 mcg/kg/min, without bolus. Increase by 20 mcg/kg/min every 20 minutes as long as HR > 90 bpm, to a maximum dose of 100 mcg/kg/min. If HR < 80 bpm and > 70 bpm, decrease infusion rate by 10 mcg/kg/min; if HR ≤ 70 bpm and > 60 bpm, decrease infusion rate by 20 mcg/kg/min. Stop study drug infusion whenever a STOP EVENT occurs. Study drug infusion is completed 3 hours after vasopressor infusions have stopped. The up-titrations can be smaller than stipulated if the clinician and/or investigator feels that a small up-titration is indicated. Up-titrations should not occur during a REASSESS VOLUME STATUS event.

Study drug should be preferentially infused centrally; where no port is available, study drug should **not be** infused into a small peripheral vein or via butterfly catheter.

STOP EVENTS:

1. If HR is ever ≤ 60 bpm, immediately stop infusion for 20 minutes, then restart at half the previous infusion rate, rounded to nearest 10 mcg/kg/min. Do not resume infusion until HR > 70 bpm.
2. If vasopressor dose increases by 0.2 mcg/kg/min norepinephrine (or equivalent) AND doubles within 60 min despite adequate volume expansion, STOP the study drug infusion. Alternatively, if the treating clinician believes that the shock is worsening significantly, STOP the study drug infusion. Do not resume without explicit approval of study physician.
3. If cardiogenic shock develops ($ScvO_2 \leq 60\%$ OR LV Ejection Fraction $\leq 25\%$ OR Cardiac Index ≤ 2.0 L/min/m²), STOP the study drug infusion. Do not resume without explicit approval of study physician.
4. If clinically apparent bronchospasm develops, STOP the study drug infusion. Do not resume.
5. If Grade 2 or Grade 3 heart block develops, immediately STOP the study drug infusion. Do not resume.

REASSESS VOLUME STATUS EVENTS:

When markers of potential preload deficit occur (urine output < 0.5 ml/kg/hr OR vasopressor dosage increase), immediately EVALUATE FOR VOLUME RESPONSIVENESS. A vasopressor dosage increase is defined as at least 0.05 mcg/kg/min absolute AND 20% relative increase in the norepinephrine (or equivalent) infusion.

Titrate vasopressors as per local practice to maintain MAP ≥ 65 mmHg. Norepinephrine is the preferred primary vasopressor.

APPENDIX 2: Constituents of the esmolol (BREVIBLOC) vehicle

Sodium Chloride, USP
Water for Injection, USP
Sodium Acetate Trihydrate, USP
Glacial Acetic Acid, USP
Sodium Hydroxide
Hydrochloric Acid

APPENDIX 3: List of nodal blocking agents

Acebutolol
Amiodarone
Atenolol
Betaxolol
Bisoprolol
Bretylum
Carvedilol
Digoxin/digitalis
Diltiazem
Disopyramide
Dofetilide
Dronedarone
Esmolol
Flecainide
Labetalol
Metoprolol
Nadolol
Nebivolol
Penbutolol
Pindolol
Procainamide
Propafenone
Propranolol
Quinidine sulfate
Sotalol
Timolol
Verapamil

APPENDIX 4.

As noted in section 10.2, investigators will report all adverse events that are serious and study drug or study procedure related to the chair of the SMC within 24 hours. The SMC and the PI will then notify the IRB.

The PI, in consultation with the chair of the SMC, will determine if a SAE has a reasonable possibility of having been caused by the study drug or procedure, as outlined in 21 CFR 312.32(a)(1). The PI, in consultation with the SMC chair, will also determine whether the event is unexpected. An adverse is considered “unexpected” if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). For this study, the esmolol (Brevibloc®) package insert serves as the investigator brochure. If a determination is made that a serious adverse event has a reasonable possibility of having been caused by the drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The PI will report all unexpected and study related deaths, SAEs, and SUSARs to the SMC and IRB within 7 days after report of the event. A written report will be sent to the SMC and IRB within 15 calendar days. The SMC will also review all adverse events and clinical outcomes during scheduled interim analyses.

A4.1. UNANTICIPATED PROBLEMS (UP)

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

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

A4.2. DETERMINING RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG OR PROCEDURES

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

- **Definitely Related:** The event follows: (a) a reasonable, temporal sequence from study drug or a study procedure; and (b) cannot be explained by the known characteristics of the patient’s clinical state or other therapies; and (c) evaluation of the patient’s clinical state indicates to the investigator that the experience is definitely related to study procedures.
- **Probably or Possibly Related:** The event should be assessed following the same criteria for “Definitely Related”. If in the investigator’s opinion at least one or more of the criteria are not present, then “probably” or “possibly” associated should be selected.

- Probably Not Related: The event occurred while the patient was receiving esmolol or undergoing study procedures 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 therapies administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

Certain serious adverse events will not require adjudication; they will always be understood to be drug-related.

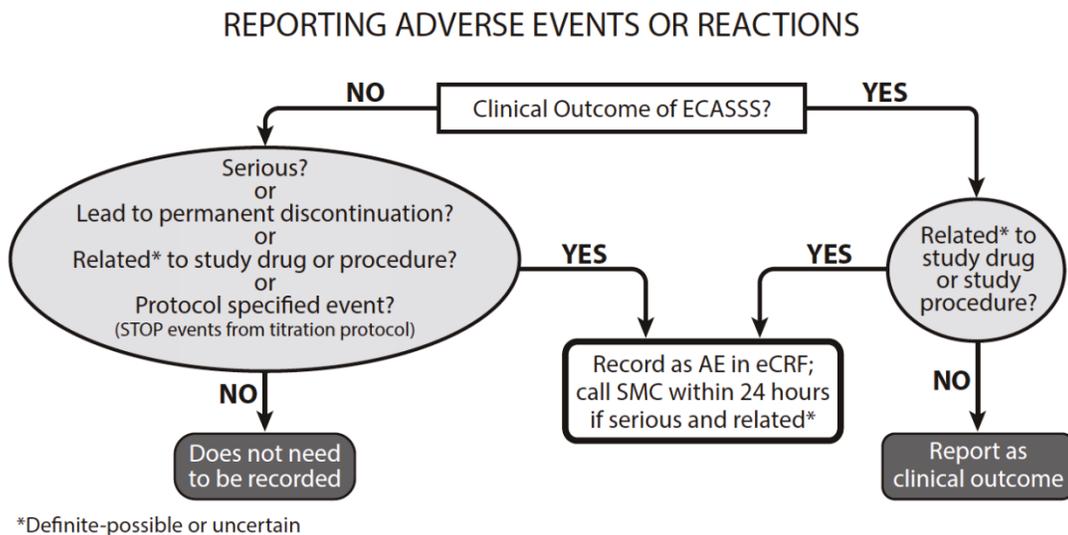
- Third-degree heart block while receiving esmolol infusion.

A4.3. CLINICAL OUTCOMES THAT MAY BE EXEMPT FROM ADVERSE EVENT REPORTING

Study-specific clinical outcomes of septic shock, as outlined in Sections 2.8 and 3.5 (Primary and Secondary Outcomes) and Section 5.1 (Assessments) are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug or the conduct of study procedures (or of uncertain relationship). The following are examples of events that will be considered study-specific clinical outcomes

- Death not related to the study drug or procedures.
- Cardiovascular events: changes in doses of vasoactive drugs or VOLUME EXPANSION events.
- Organ dysfunction events: changes in the SOFA score and its constituents.
- Cardiogenic shock that does not resolve 20 minutes after cessation of esmolol

A4.4. DECISION TREE FOR REPORTING ADVERSE EVENTS



Adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. Epub 2012 May 22. PubMed PMID: 22616830 with permission of Dr. Thompson.

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