

**PROTOCOL TITLE:** Angiotensin II as a first-line vasopressor for distributive shock for heart transplant and left ventricular assist device implantation recipients: A Pilot Study

**PRINCIPAL INVESTIGATOR:**

*Choy Lewis, MD*  
 Department of Anesthesiology  
 Email : [Choy.Lewis@nm.org](mailto:Choy.Lewis@nm.org)

**CO-INVESTIGATORS:**

*Duc Thinh Pham, MD*  
 Department of Surgery  
 Telephone Number: 312-695-3121  
 Email: [dpham1@nmh.org](mailto:dpham1@nmh.org)

*Abbas Al-Qamari*  
 Department of Anesthesiology  
 Email: [Abbas.Al-Qamari@nm.org](mailto:Abbas.Al-Qamari@nm.org)

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**STUDY SUMMARY:**

Investigational Agent(s) (Drugs or Devices)	Giapreza (Angiotensin II)
IND / IDE / HDE #	N/A
Indicate Special Population(s)	<input type="checkbox"/> Children <input type="checkbox"/> Children who are wards of the state <input type="checkbox"/> Adults Unable to Consent <input type="checkbox"/> Cognitively Impaired Adults <input type="checkbox"/> Neonates of Uncertain Viability <input type="checkbox"/> Pregnant Women <input type="checkbox"/> Prisoners (or other detained/paroled individuals) <input type="checkbox"/> Students/Employees
Sample Size	80
Funding Source	La Jolla
Indicate the type of consent to be obtained	<input checked="" type="checkbox"/> Written <input type="checkbox"/> Verbal/Waiver of Documentation of Informed Consent <input type="checkbox"/> Waiver of HIPAA Authorization <input type="checkbox"/> Waiver/Alteration of Consent Process
Site	<input type="checkbox"/> Lead Site (For A Multiple Site Research Study) <input type="checkbox"/> Data Coordinating Center (DCC)
Research Related Radiation Exposure	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
DSMB / DMC / IDMC	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **OBJECTIVES:**

Patients undergoing implantation of a durable left ventricular assist devices (LVAD) or a heart transplantation are at increased risk for cardiac vasoplegia. Vasoplegia during or after LVAD placement or heart transplantation increases mortality and end organ dysfunction. The prognosis is especially poor for patients with refractory hypotension, despite high doses of vasopressors. Catecholamine vasopressors and vasopressin, which are often used as first line vasopressor therapy, are also independent risk factors for end organ dysfunction. Existing data point to total catecholamine dose, cumulative time spent with hypotension, volume overload, need for blood transfusion as contributing factors.

In patients with distributive shock in the intensive care unit, angiotensin II has been shown to reduce total catecholamine dose over 24 hours and the cumulative time spent with hypotension. This study will evaluate the following specific aims:

**Aim 1:** To evaluate whether first line use of angiotensin II affects total catecholamine vasopressor dose over the first 24 hours

**Hypothesis:** Use of angiotensin II as a first line agent reduces total catecholamine vasopressor dose over the first 24 hours

**Aim 2:** To assess the impact of use of angiotensin II as a first line agent on cumulative time spent with MAP<70mmHg

**Hypothesis:** Use of angiotensin II as a first line agent reduces cumulative time spent with MAP<70mmHg

**Aim 3:** To assess the impact of use of angiotensin II as a first line agent on fluid overload

**Hypothesis:** Use of angiotensin II as a first line agent reduces volume overload.

**Aim 4:** To assess the impact use of angiotensin II as a first line agent on need for blood transfusion

**Hypothesis:** Use of angiotensin II as a first line agent reduces the need for blood transfusion.

**Aim 5:** To assess the impact of use of angiotensin II as a first line agent on end organ dysfunction (Time to extubation, Acute kidney injury within 48 hours, Stroke, New tachyarrhythmia).

**Hypothesis:** Use of angiotensin II as a first line agent reduces end organ dysfunction.

**Aim 6:** To assess the impact of use of angiotensin II as a first line agent on need for vasoplegia rescue therapy (methylene blue, vitamin B12, Vitamin C, steroid).

**Hypothesis:** Use of angiotensin II as a first line agent reduces the need for vasoplegia rescue therapy.

**Aim 7:** To assess the impact of use of angiotensin II as a first line agent on 30-day mortality.

**Hypothesis:** Use of angiotensin II as a first line agent reduces 30-day mortality.

**Aim 8:** To assess the impact of use of angiotensin II as a first line agent on ICU and hospital length of stay.

**Hypothesis:** Use of angiotensin II as a first line agent reduces ICU and hospital length of stay.

**Aim 9:** To assess the impact of use of angiotensin II as a first line agent on allograft rejection (heart transplant population only).

**Hypothesis:** Use of angiotensin II as a first line agent reduces allograft rejection.

**BACKGROUND:**

Vasoplegic syndrome, also known as vascular hyporesponsiveness and cardiac vasoplegia, is characterized by severe arterial hypotension and decreased systemic vascular resistance. Patients have increasing vasopressor requirement, in the setting of low or normal filling pressures and normal to high cardiac output. In patients who undergo cardiopulmonary bypass (CPB), the reported incidence is 5-25% (1,2). Heart transplantation is a risk factor for vasoplegic syndrome, with a reported incidence between 11% and 54%. (3,4,5) One study recently found an incidence of 49% for patients after left ventricular assist device (LVAD) implantation. (6) In that same study, Tecson et al. showed that patients who developed moderate to severe vasoplegia after LVAD implantation had a > 2-fold increase risk of mortality. They also found that major bleeding, respiratory failure, acute right heart failure and hospital length of stay increased with vasoplegia severity. (6) Several mechanistic pathways have been implicated in the pathogenesis of vasoplegic syndrome. Among these are the overproduction of inducible nitric oxide synthase, activation of ATP-dependent potassium channels, down regulation of vasopressin receptors and desensitization of angiotensin receptors.

Vasoplegia, during or following cardiac surgery, is a life-threatening condition that is characterized by poor organ perfusion and may progress to multi-organ failure. Several studies have reported increased mortality in patients with vasoplegia following cardiac surgery when compared to similar patients without vasoplegia. (7,8,9) The prognosis is especially poor for patients with refractory hypotension, despite high doses of vasopressors. (10,11,12) If left untreated, severe vasoplegia is universally fatal. Current management strategies include administration of fluids and vasopressor therapy. Catecholamine vasopressors, mainly norepinephrine, are used as first line agents followed by vasopressin. Methylene blue and/or hydroxocobalamine and/or angiotensin are then added as third line agents in the setting of persistent hypotension or to help with decreasing the amounts of norepinephrine and vasopressin. The dose of norepinephrine at which vasopressin is initiated is arbitrary as is the decision to initiate a third line agent. The choice of third line agent is also arbitrary.

High doses of catecholamine vasopressors, as well as vasopressin, may cause serious side effects such as peripheral or mesenteric ischemia. (13,14) In addition, such vasopressors increase oxidative stress, interfere with cellular energy metabolism and modulate the inflammatory response. (15) Conceptually it makes sense that strategies aimed at reducing the need for catecholamine vasopressors and vasopressin should at least reduce these side effects and improve outcomes. To date, data comparing mortality with the use of different classes of vasopressors, in various types of shock, have been equivocal. A recent Cochrane analysis concluded that there was not sufficient evidence to prove that any one vasopressor was superior to others in terms of mortality and that the choice of a specific vasopressor may, therefore, be individualized and left to the discretion of treating physicians. (16)

Data comparing the use of different classes of vasopressors for cardiac vasoplegia during or after heart transplantation and LVAD implantation are lacking. The ATHOS-3 trial showed that angiotensin II can be used to increase mean arterial pressure (MAP) in patients with catecholamine vasopressor resistant distributive shock and has a catecholamine vasopressor sparing effect. (17) This has stimulated renewed interest in angiotensin II as a vasopressor for vasodilatory shock. It is still not known whether angiotensin II has a catecholamine vasopressor sparing effect during or after heart transplantation or LVAD implantation, whether angiotensin II reduces the degree of hypotension that can be seen with these patients and if angiotensin II reduces the overall amount of time spent with MAP below acceptable target. Recent data have identified plasma renin level and plasma renin activity as markers of tissue perfusion

and prognosticating factors in patients who are critically ill. It is not known whether use of angiotensin II alters renin activity in patients who receive heart transplantation or LVAD.(18,19)

## STUDY DESIGN

This is a single-center, randomized, double-blind, placebo-controlled pilot study. A total of 40 patients who develop distributive shock, intra-operatively or post-operatively within 48 hours of heart transplant or left ventricular assist device placement will be enrolled. Participants will be randomized to angiotensin II vs. placebo plus standard of care, as a first line agent for vasoplegia. Two groups of patients will be enrolled:

- Group A: Heart Transplant (10 control, 10 treatment)
- Group B: LVAD implant (10 control, 10 treatment)

## STUDY ENDPOINTS:

### *Primary Endpoint*

1. Total catecholamine dose for first 24 hours (measured in norepinephrine equivalents) after distributive shock is first diagnosed.

### *Secondary Endpoints*

1. Cumulative time spent with MAP < 70 mmHg within the first 24 hours after distributive shock is first diagnosed.
2. Time to extubation
3. Acute kidney injury within 48 hours as Staged by KDIGO Creatinine Criteria:
  - a. Stage 1: Creatinine increase by 0.3 or 1.5-1.9 times preoperative value
  - b. Stage 2: 2.0-2.9 times preoperative value
  - c. Stage 3: 3 times preoperative value or creatinine >4 or initiation of RRT
4. Stroke diagnosed by a neurologist
5. New tachyarrhythmia (SVT, atrial fibrillation or atrial flutter) within first 24 hours.
6. 30-day mortality
7. ICU/hospital length of stay
8. Units of blood transfused within the first 24 hours
9. Fluid overload over first 24 hours (net fluid balance divided by body weight)
10. Need for vasoplegia rescue therapies (methylene blue, vitamin B12, Vitamin C, steroids)
11. Allograft rejection (heart transplant population only).

### *Exploratory Endpoint*

1. Change in renin activity level

## STUDY POPULATION

All inclusion criteria and no exclusion criteria must be met for participation in the study to proceed. The study population therefore includes patients diagnosed with distributive shock at Northwestern Medicine. Subjects will be consented and followed by the study team intra-operatively through discharge. An assessment will be done at post-operative day 30 for each participant to assess 30-day mortality. We plan to enroll 40 participants over 18 months.

### **Treatment Management**

For this investigation, distributive shock will be defined as MAP less than 55 mmHg on cardiopulmonary bypass (CPB)R, MAP less than 70 mmHg before or after CPB, or systemic vascular resistance (SVR) less than 800 dynes/cm/sec<sup>5</sup> with cardiac index (CI) greater than 2.0L/min/m<sup>2</sup> and clinically determined euvolemia.

Current standard of care for vasoplegia at our institution is as follows:

- Norepinephrine for first line agent
- Vasopressin added as needed for second line agent
- Methylene and/or hydroxocobolamine as a third line agent
- Angiotensin II as fourth line agent

To avoid the ill effects of distributive shock, we maintain MAP > 55 mmHg on CPB and obtain MAP > 70 mmHg without CPB utilizing vasopressors in patients with adequate volume resuscitation and cardiac function. Additionally, standard practice is to get MAP > 75 mmHg 5 minutes prior to separating from CPB to avoid below target MAP post-CPB.

### **Inclusion Criteria:**

Patients must meet *all* of the following criteria:

1. Patients (18 years of age or older)
2. Onset of distributive shock within 48 hours after heart transplantation or VAD placement at Northwestern Memorial Hospital. Distributive shock defined as MAP less than 55mmHg on CPB, MAP less than 70mmHg before or after CPB, or systemic vascular resistance (SVR) less than 800 dynes/cm/sec<sup>5</sup> with cardiac index (CI) greater than 2.0L/min/m<sup>2</sup> and clinically determined euvolemia.

### **Exclusion Criteria:**

Patients should *not* have any of the following criteria:

1. Patients without distributive shock,
2. Women who are pregnant or breastfeeding.
3. Patients who do not receive the study drug as a first line agent for distributive shock
4. Allergy to angiotensin II, angiotensin II or another vasopressor being used at the time of presentation to the operating room
5. Preexisting distributive shock
6. Preexisting thromboembolic disease
7. Patients who are unwilling to provide consent

### **PROCEDURES INVOLVED**

Patients will be consented preoperatively prior to the onset of distributive shock, for the possibility of being included in the study, if they meet all other criteria for the study. If they develop distributive shock intraoperatively or postoperatively and still meet all exclusion and inclusion criteria for the study, they will be enrolled. Written subject informed consent will be obtained prior to any study-related procedures. At the time of consent staff will interview participants and review necessary medical records.

After the subject has agreed to participate in the study and signed the ICF, the following will be completed to determine whether the participant meets all pre-operative study entry criteria:

- Review of medical history and inclusion/exclusion criteria
- Review of concomitant medications
- Vital signs

Enrolled subjects (those randomized) will be assigned a unique participant ID. If during surgery participants develop distributive shock they will be randomly assigned to receive angiotensin infusion or placebo infusion. Randomization will be done by the Investigational Drug Service (IDS) at Northwestern Memorial Hospital. The study drug will be prepared and sent to the operating room at the beginning of the case. Titration of study medication will be according to Treatment Management section below.

### **Study Drug Administration (Day 0)**

On the day of the procedure subjects developing distributive shock will be randomized (1:1) to receive either study drug or placebo. Administration will be as follows:

#### *Management of patients not on CPB and on CPB (but not in preparation for separation from CPB)*

In patients who develop distributive shock, the study drug (Angiotensin II or placebo) will be started at 5 ng/kg/min and titrated in 5-10 ng/kg/min increments up to 40ng/kg/min for mean arterial pressure (MAP) greater than 70 mmHg for patients not on CPB or for MAP < 55 mmHg while on CPB. The dose of the study drug will be increased every 5 minutes by 5-10ng/kg/min increments up to 80ng/kg/min in an attempt to achieve target MAPs.

If the MAP remains less than target despite study drug administration of 40 ng/kg/min, norepinephrine will be started at 0.05mcg/kg/min and titrated up to 0.12mcg/kg/min for target MAP of 70 mmHg when the patient is not on CPB and target MAP of 55 mmHg while on CPB. If the MAP is still less than target, vasopressin, starting at 0.0004 –0.0006 units/kg/min, will be added and titrated up to 0.0012-0.002 units/kg/min. Methylene blue 100mg and/or hydroxocobalamine 5g (up to 10g) and/or vitamin C 1500mg will be administered.

#### *Management of patients in Preparation for Separation from CPB*

If no vasopressor is being used at the time of cross clamp removal, study drug will be started at 5 ng/kg/min and titrated up to 40 ng/kg/min for goal MAP > 75 mmHg prior to separation from CPB. The dose of the study drug will be increased every 5 minutes by 5-10ng/kg/min increments up to 80ng/kg/min in an attempt to achieve target MAPs. If MAP remains less than 75mmHg despite study drug at 40ng/kg/min, norepinephrine will be started at 0.05mcg/kg/min and titrated up to 0.12mcg/kg/min for target MAP of 75 mmHg. If the MAP is still less than 75 mmHg, vasopressin, starting at 0.0004 –0.0006 units/kg/min, will be added and titrated up to 0.0012-0.002 units/kg/min. Methylene blue 100mg and/or hydroxocobalamine 5g (up to 10g) and/or vitamin C 1500mg will be administered. Further increases in the dose of any vasopressor or the addition of another vasopressor will be per the provider's discretion.

### **Permitted dose adjustments and interruptions of treatment**

If the MAP remains less than target once study drug is being administered at 40 ng/kg/min, the following will be added (Figure 1):

- 2<sup>nd</sup> Line Agent: norepinephrine will be started at 0.05mcg/kg/min and titrated up to a maximum of 0.12mcg/kg/min to achieve target MAP.

- 3<sup>rd</sup> Line Agent: vasopressin, starting at 0.0004 –0.0006 units/kg/min, will be added and titrated up to 0.0012-0.002 units/kg/min to achieve target MAP.
- 4<sup>th</sup> Line Agent: Methylene blue 100mg or hydroxocobolamine 5g (up to 10g) will be given.

Further increases in the dose of any vasopressor or the addition of another vasopressor will be per the provider's discretion. Inotropes will be initiated and titrated per the discretion of the providers. Epinephrine will be considered a vasopressor at doses greater than 0.05mcg/kg/min. At doses less than 0.05mcg/kg/min, epinephrine will be considered an inotrope only.

Providers may deviate from this protocol at any point for safety reasons, per their discretion. The dose of a medication and timing for initiation or cessation of use of the drug will be per the provider's discretion. Once initiated as a part of this study, the study drug should be continued for as long as it is deemed to be necessary to maintain target blood pressure. If a patient is not already on the study drug and angiotensin II has to be initiated greater than 48 hours postoperatively (after the primary or any subsequent surgery), the study drug should not be administered. In that situation, angiotensin II should be directly requested from the pharmacy.

All medications, including dose adjustments and add-on therapies, will be recorded. Timing of study medication will be recorded.

#### **Preoperatively (day of surgery)**

- Renin activity level

#### **Postoperatively (on arrival to the ICU)**

- Renin activity level

#### **24 Hours post procedure**

- Review of cardiovascular medications
- Use of blood products
- Fluid volume assessment
- Adverse event assessment (AKI): All creatinine values done for first 24 hour
- Adverse event assessment (Acute CVA): Diagnosed/documented by neurologist
- Adverse event assessment (Onset of new tachyarrhythmia): Documented in note by ICU resident, fellow or attending
- Adverse event assessment – other serious events (major blood loss, need for reoperation)
- Adverse event assessment (Allograft rejection): Diagnosed/documented in cardiac surgeon or ICU attending note (heart transplant only)

#### **48 Hours post-procedure**

- Adverse event assessment (AKI): All creatinine values done for first 24 hour
- Adverse event assessment (Acute CVA): Diagnosed/documented by neurologist. If present, what is the basis for diagnosis (symptoms vs CT vs MRI) per neurologist's note.
- Adverse event assessment – other serious events (major blood loss, need for reoperation)

**30 Days post-procedure**

- Mortality

**Variable Time post-procedure**

- Time to Extubation
- Hospital/ICU length of stay

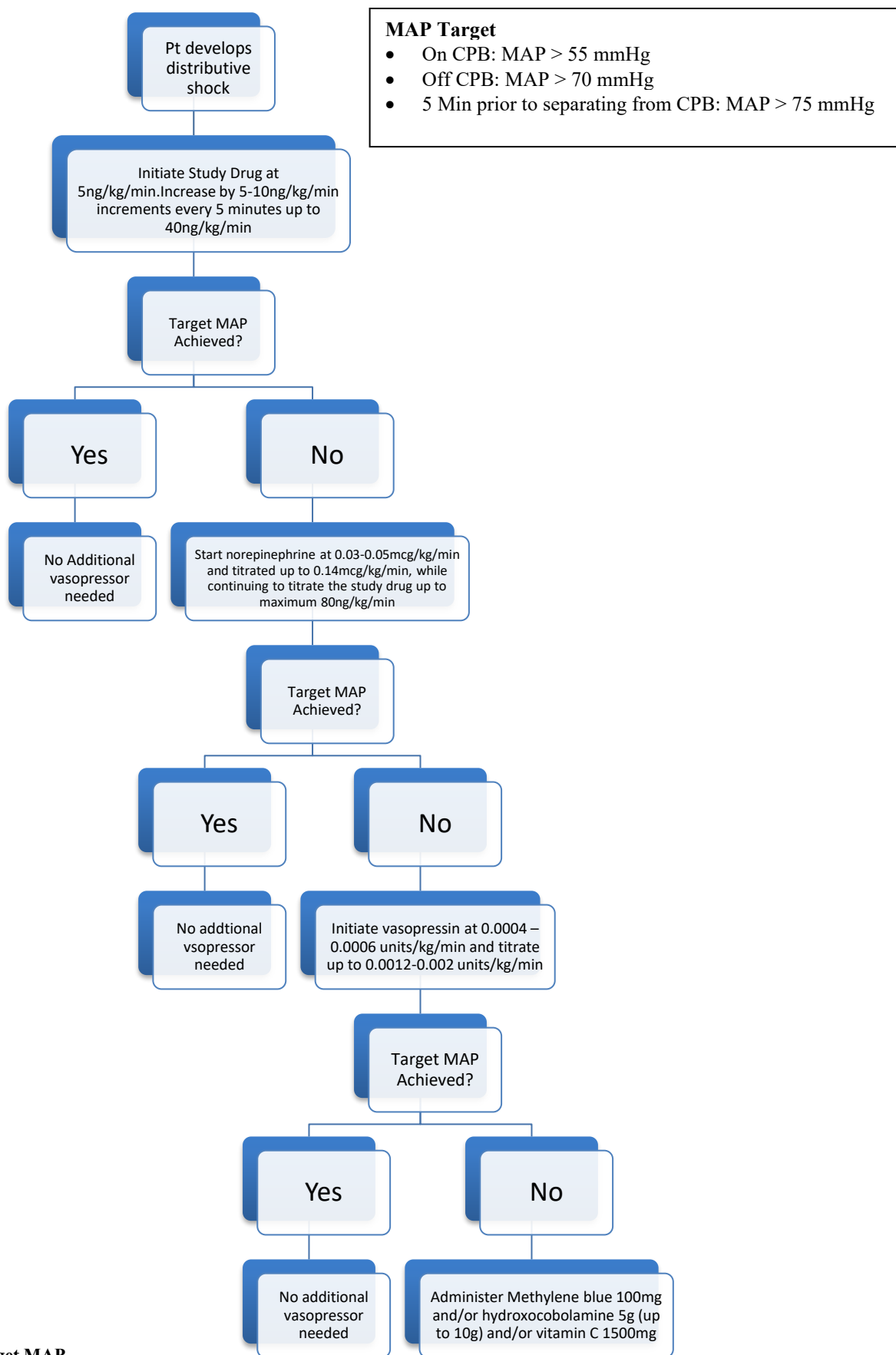


Figure 1. Maintaining Target MAP

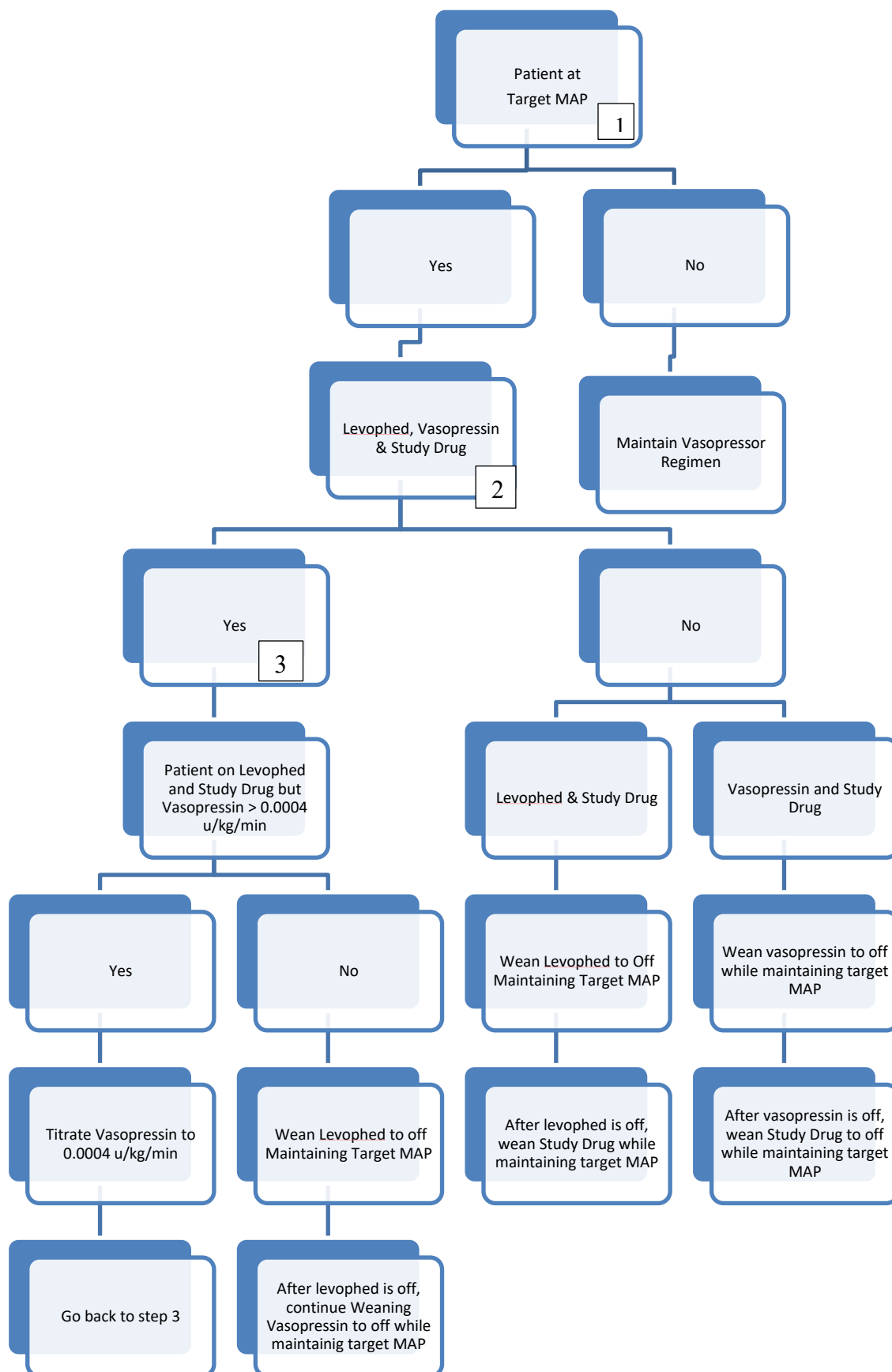


Figure 2. De-escalating algorithm

## **DESCRIPTION OF STUDY MEDICATION (GIAPREZA)**

Northwestern Medicine Investigational Pharmacy will be responsible for preparation and dispensing of GIAPREZA. No alterations will be made to the formulary, route of administration or packaging of GIAPREZA for this study. Refer to Prescribing Information for GIAPREZA in Appendix A.

- Product Name: GIAPREZA (angiotensin II) (La Jolla Pharmaceutical)
- How Supplied:
  - 2.5 mg/mL vial: NDC 68547-501-02: A carton of one 1 mL single dose vial containing 2.5 mg angiotensin II (as a sterile liquid).
  - 5 mg/2 mL vial: NDC 68547-002-05: A carton of one 2 mL single dose vial containing 5 mg (2.5 mg/mL) angiotensin II (as a sterile liquid).

GIAPREZA (angiotensin II) is an FDA approved vasoconstrictor medication used to increase blood pressure in adults with septic or other distributive shock. GIAPREZA must be administered as an intravenous infusion and is available in 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL) vials. Use in this study will be according to the prescribing information outlined in the FDA approved package insert. All dosages prescribed and dispensed to the patient and all dose changes during the study will be recorded on the Dosage Administration Record according to institutional practice.

## **DATA AND SPECIMEN BANKING**

Data will be collected from the electronic medical record daily. The data will be collected by the dedicated research study team. A data sheet will be completed by research personnel and transferred to a secured database, REDCap. Subjects' identity will be guarded by assigning a unique participant ID, which is only known by the research team. A screening and enrollment log will be maintained by the study coordinator, which connects with study ID numbers and includes participant names, medical record number, age, date of procedure, enrolled (yes or no), and reason why they did not want to participate (if applicable). This log will be maintained electronically in the Clinical Trials Unit. Access to REDCap is password protected and only available to study investigators and authorized study personnel.

## **SHARING RESULTS WITH PARTICIPANTS**

All participants and involved parties (clinical personnel including investigators, patients and their families, etc.) will remain blinded for the duration of the study. Once enrollment is closed and all patients have completed the study, randomization will be unblinded.

All clinical parameters will be shared with participants according to standard practice of the clinician caring for the patient.

## **Unblinding Procedures**

The study team will be blinded to the randomization assignment unless a participant has a clinical need to know their randomization assignment. The decision to un-blind will be at the discretion of the study PIs and only if un-blinding would change clinical care. Unblinding for safety reasons will be recorded in study records and it will be reported to the IRB and the funding sponsor at the time of continuing review.

## **VULNERABLE POPULATIONS**

Vulnerable populations will not be enrolled in this study.

## **PARTICIPANT POPULATION(S)**

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Adults	60	40 (20 VAD, 20 Transplant)
Study-wide		N/A	N/A
Total:	Adults	60	40

## RECRUITMENT METHODS

Patients will be recruited by a treating member of the clinical team. Consent can occur preoperatively in clinic, hospital room (ICU or floor), or the preoperative holding area prior to the procedure.

## COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

No compensation will be provided to participants.

## WITHDRAWAL OF PARTICIPANTS

Subjects may voluntarily withdraw from the study at any time without reason. The investigator or designee shall capture reason for participant withdrawal. In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time, for any reason. In the event a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

The PI may also remove participants from the study for emergent conditions such as medication intolerance.

## RISKS

### Study Medication Risks

No alterations will be made to the formulary or route of administration of GIAPREZA for this study. The most common adverse reactions reported in greater than 10% in GIAPREZA treated patients were thromboembolic events.

**Table 1.** Adverse reactions occurring in  $\geq 4\%$  of patients treated with GIAPREZA and  $\geq 1.5\%$  more often than in placebo

<b>Adverse Event</b>	<b>GIAPREZA N=163</b>	<b>Placebo N=158</b>
Thromboembolic events <sup>a</sup>	21 (12.9%)	8 (5.1%)
Deep vein thrombosis	7 (4.3%)	0 (0.0%)
Thrombocytopenia	16 (9.8%)	11 (7.0%)
Tachycardia	14 (8.6%)	9 (5.7%)
Fungal infection	10 (6.1%)	2 (1.3%)
Delirium	9 (5.5%)	1 (0.6%)
Acidosis	9 (5.5%)	1 (0.6%)
Hyperglycemia	7 (4.3%)	4 (2.5%)
Peripheral ischemia	7 (4.3%)	4 (2.5%)

<sup>a</sup> Including arterial and venous thrombotic events

Study medication will be administered and titrated by trained and qualified cardiologists or clinical personnel. Appropriate care will be provided for any adverse event. Any unanticipated, serious adverse events will be reported to the Institutional Review Board.

### **Treatment Risks**

There is a risk that patients will remain hypotensive while the study drug is being titrated or if randomized to placebo. Other vasopressors will be initiated per protocol to prevent excessive hypotension due to utilization of the study drug. To avoid unnecessary hypotension while awaiting the study drug, the study drug will be available in the operating room at the beginning of the case. Providers can also deviate from the protocol per their discretion to prevent unnecessary risk to patients.

### **HUMAN SUBJECTS PROTECTION**

This study will be conducted in compliance with the current ICH E6 GCP, the ethical principles of the Declaration of Helsinki, current FDA GCP guidelines, and any additional national or IRB/IEC required procedures, whichever represents the greater protection for the individual.

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). The study will not start before the IRB gives written approval in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval.

The Investigator is responsible for informing the Northwestern University IRB of any changes made to the protocol, and to advise the IRB, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB of any significant AEs that occur during the study according to Northwestern University IRB requirements.

### **NEW INFORMATION INFLUENCING THE SUBJECT'S CONSENT**

The investigator/sub-investigator will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness

to continue participation in the study (e.g., report of serious adverse events). The communication should be documented and it should be confirmed whether the subject is willing to remain in the study or not.

### **POTENTIAL BENEFITS TO PARTICIPANTS**

The use of GIAPREZA as a first line treatment for distributive shock may help treat these patients and reduce fatality in this population.

### **DATA COLLECTION**

Clinical data collected by medical records review daily and will include data such as demographics, medical history, risk factors, symptoms, surgical procedure(s), hospitalization information, medications, hemodynamic data, laboratory results, morbidity and mortality. Data elements to be captured are listed in Appendix B.

Data will be collected by trained research staff using source documents and CRFs. Source and CRFs will be entered into a REDCap data management system (DMS). Participants will be assigned a Participant ID “PID” for use on CRF data collection in for entry into the DMS to protect and ensure confidentiality.

### **DATA MANAGEMENT**

All data for analysis will be stored in REDCap (Research Electronic Data Capture), a secure, web-based application for building and managing online data capture for research studies. Northwestern University is a member of the REDCap consortium. Northwestern University Biomedical Informatics Center (NUBIC) hosts and supports the development and maintenance of the database.

Electronic signature procedures comply with the CFR Title 21 Part 11 and the ICH Guidelines for Good Clinical Practice (GCP). Research personnel will need a Northwestern NetID and password to access RedCap to prevent unauthorized access. Access to information is based on the individual’s roles and responsibilities.

Subjects who are recruited into this study will be entered in Study Tracker as per Northwestern University policy, by the study coordinator or other study staff.

### **CONFIDENTIALITY**

The confidentiality of the subjects' identities shall be well protected consistent with local and national regulations. In cases where study data is published or shared with other institutions, data will be de-identified. Publications and reports will never include identifiable information, such as name, social security number, address or medical record number in order to maintain patient’s identity.

The software that will be used to manage this project is REDCap, which is overseen by Northwestern University Biomedical Informatics Center (NUBIC). Data will be accessible only to those listed as study team members on the IRB application and stored indefinitely. Authorized study personnel will be assigned a unique password and only that individual should access subject records under that password.

An enrollment log identifying each subject with his/her assigned unique participant ID, subject initials, gender, date of consent and date of surgery will be maintained by the study coordinator. Enrollment data will be entered into the study spreadsheet maintained by the Clinical Trials Unit (Arkes Pavilion, Suite 1700) housed on an NM server.

The study data will be stored indefinitely. A de-identified data set may be shared with the funding sponsor.

### **RECORDS RETENTION**

Any paper Data Collection Forms (DCF) will be kept in a secure (locked) location within the authorized personnel office or the Bluhm Cardiovascular Institute Clinical Trials Unit. Only authorized research personnel will have access to these files. All records produced or collected in connection with this project, including data collection forms shall be retained for a minimum of **three (3) years** from the date of the study closure (often marked by a final progress report). When ready for destruction paper documents will be destroyed by shredding and will be performed in a manner that ensures information cannot be reconstructed.

### **PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS**

Study progress and safety will be reviewed at least monthly including patient recruitment and adverse events. At the time of annual review a report will be compiled and include a summary of adverse events. In addition, the annual report will address whether rates of adverse events are consistent with pre-study assumptions, whether all study participants met entry criteria, whether continuation of the study is justified in order to get additional data to accomplish the aims of the study, and conditions whereby the study may be terminated prematurely. The annual report will be sent to the IRB and the sponsoring company.

All safety events related to GIAPREZA will be reported to FDA per standard safety, pharmacovigilance procedures at NMHC.

### **PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS**

Information will be shared only with necessary research personnel. Specifically, unless required by law, only the study investigator, members of the investigator's staff, the Northwestern University IRB, representatives of the FDA, and other international regulatory agencies will have the authority to review study records.

All paper records are kept in a secure area in Bluhm Cardiovascular Institute Clinical Trials Unit (Arkes Pavilion, Suite 1700) that is not open to the public. Electronic research data will be on password protected computers; only authorized personnel can access the data. Subjects will receive unique study code numbers; any information that is collected for a subject on a CRF will have the subject's unique study code number and initials.

### **COMPENSATION FOR RESEARCH-RELATED INJURY**

No compensation will be provided for subject injury. Study medication is being used according to FDA approved labeling. Any complications will be billed to the patient and/or insurance in the usual way.

### **ECONOMIC BURDEN TO PARTICIPANTS**

Participants in this study will not be held responsible for any research-related costs. The participant will remain responsible for any costs associated with standard of care procedures. The study medication will be provided at no cost.

## **CONSENT PROCESS**

This study will be conducted in compliance with current ICH E6 GCP pertaining to informed consent, and current CFR (Title 21, Parts 50). To participate in the study, the subject must sign and date the ICF after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits, before initiation of any study-related procedures. A copy of the signed ICF must be provided to the subject. Signed ICFs must remain in the subjects' study files and be available for verification.

Informed consent must be obtained from each patient prior to conducting any study activities beyond standard of care, by using the informed consent form (ICF) approved by the Northwestern University IRB. Consent will take place at Northwestern Memorial Healthcare facilities. Participants may be informed of the research study on an occasion prior to signing the consent form.

The procedures and policies of "SOP: Informed Consent Process for Research (HRP 090)" will be followed during the consent process. Accordingly, the most recently approved version of the consent form will be used, a copy of this form will be provided to the potential participant, and the potential participant will be given as much time as they need to review the form independently. The individual obtaining consent will then review all contents of the consent form with the potential participant and if the participant prefers, any family or friends that they would like to be involved. Time will be given to the participant (and if applicable, friends/family) to ask any questions and clarification will be given by the individual obtaining consent.

## **NON-ENGLISH SPEAKING PARTICIPANTS**

Participants who do not speak English will not be enrolled in this project.

## **PROTECTED HEALTH INFORMATION (PHI AND HIPAA)**

A participant's privacy and confidentiality will be respected throughout the study. Authorization will be obtained from each research subject, i.e. specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI. All data will be strictly confidential. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

## **QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE**

A multidisciplinary approach will allow for successful completion of this research study. The study PI is a cardiothoracic surgeon specializing in heart transplantation and LVAD placement. His collaborating co-investigators are comprised of anesthesiologists who monitor patient medications and hemodynamics during heart transplant and LVAD procedures. The Clinical Trials Unit has dedicated regulatory and

research personnel that will be available to assist with the regulatory, recruitment, data collection and management aspects of this study.

All investigators are highly experienced and have contributed to this proposal. We will meet as a team regularly to review data collection, data analyses, and other reports. This team has coalesced extremely well in preparation of this project, and we anticipate no problems in performing the work that we propose.

## **STUDY FINANCES**

### **Funding Source**

This study is financed through a contract with Jolla Pharmaceuticals. Jolla Pharmaceuticals is considered the funding sponsor who will provide financial support to conduct the study and the study medication, GIAPREZA, free of charge.

### **Conflict of Interest**

All Northwestern University Investigators will follow the Northwestern University [Policy on Conflicts of Interest Related to Research](#).

### **Participant Stipends or Payments**

Participants will not receive payment for their participation in this study.

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## APPENDIX A

GIAPREZA Prescribing Information attached separately

## APPENDIX B

### Data Collection

- Demographic data: age, height, weight, sex, ethnicity
- Medical History: cardiovascular history, past surgical history, medications, allergies
- Surgical procedure details (heart transplant or LVAD placement +/- other surgical procedure)
- Hemodynamic data: blood pressure (non-invasive and invasive), heart rate, oxygen saturation (SpO<sub>2</sub>) cardiac output, cardiac index, SvO<sub>2</sub>, bilateral cerebral oxygen saturation
- Total catecholamine (Epinephrine, norepinephrine, ephedrine) dose for first 24 hours (measured in norepinephrine equivalents) after distributive shock is first diagnosed.
- Total dose of other vasopressors (vasopressin, methylene blue, vitamin B12 or hydroxocobolamine, steroids, and Vitamin C used within the first 24 hours after distributive shock was diagnosed
- Cumulative time spent with MAP < 70 mmHg within the first 24 hours after distributive shock is first diagnosed.
- Time to extubation (in minutes)
- All creatinine values within the first 48 hours after the procedure.
- Adverse Events including stroke diagnosed by a neurologist
- New tachyarrhythmia (SVT, atrial fibrillation or atrial flutter) within first 24 hours after distributive shock is first diagnosed
- 30-day mortality
- ICU/hospital length of stay
- Units of blood transfused within the first 24 hours after distributive shock is first diagnosed
- Fluid overload over first 24 hours (net fluid balance divided by body weight) after distributive shock is first diagnosed
- Allograft rejection (heart transplant population only)
- Preoperative & postoperative renin activity level