B-lines Lung Ultrasound Guided ED Management of Acute Heart Failure (BLUSHED-AHF) Pilot Trial

Principal Investigator: Peter S. Pang MD

IND/IDE Sponsor: NA

Funded by: NHLBI

Version Number: v.8.1

Jan 23 2018

Version 7.2

- The overall protocol now matches the specific LUS protocol.
- The time window for blood draws was clarified. The first draw needed to occur during the ER stay. The final pre-discharge blood draw needed to occur as soon as possible prior to discharge.
- Reassessments have been modified. Rather than every 2 hours in the ED, a minimum of two assessments will occur. The first within 2-4 hours after first treatment. The second 2-4 hours after the first OR pre-discharge from the ED, whichever occurs first. The protocol figure has thus been modified accordingly, as well as the LUS imaging times and other places within the protocol.
- The schedule of events has also been updated to reflect the aforementioned changes.

Version 7.6

- Changed the time stamp to reflect first recorded time stamp patient was placed in a room to be seen by a physician or the first time AHF treatment is given, whichever comes first. The second part was added in case treatment is given by a triage physician.
- Clarified dosing of Lasix in protocol to a maximum dose of 200 mg at any one time.
- Estimated urine output is acceptable.
- Clarifications to the protocol re: treatment per the usual care arm.
- Windows for follow-up calls clarified.

Version 7.8

1. Clarified the name of time of each scan (T24 changed to HD2) to ensure image nomenclature protocol and the study protocol are the same.

- Dropped urine output guidance from the treatment protocol.
- Extended the time window of the study to 6 hours post-enrollment, irrespective of patient location. However, this will NOT be a protocol violation if circumstances judged by the investigator do not allow for ED-guided treatment to continue.
- Editing and clarifications were also added.

Version 7.9

- Clarifies first dose of diuretic and difference between treatment arms.
Version 8.1

Fixed discrepancy between DSMB charter and protocol regarding an interim analysis.

The initial protocol used time from first ultrasound as the baseline assessment. However, per the initial revision listed above, we changed to time of first treatment. We did this because time of order of treatment and actual receipt of treatment were potentially large time windows. We wanted to avoid repeating US before any treatment was received. Unfortunately, this has led to more confusion as occasionally, patients receive treatment before the first US. How to account for this time has been challenging. As a result, we will revert to the original protocol; time of first US as the benchmark.
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LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHF</td>
<td>Acute Heart Failure</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>HF</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>EP</td>
<td>Emergency Physician</td>
</tr>
<tr>
<td>LUS</td>
<td>Lung ultrasound</td>
</tr>
<tr>
<td>DAOOH</td>
<td>Days alive and out of hospital</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation (positive pressure ventilation)</td>
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<tr>
<td>NTG</td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>SL</td>
<td>Sub-lingual</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute Kidney Injury</td>
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<tr>
<td>WRF</td>
<td>Worsening renal function</td>
</tr>
<tr>
<td>WHF</td>
<td>Worsening heart failure</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>Hgb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Hct</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>IEC</td>
<td>Institutional Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>CTSL</td>
<td>Clinical and Translational Sciences Lab at IU</td>
</tr>
<tr>
<td>IU</td>
<td>Indiana University</td>
</tr>
<tr>
<td>IWRS</td>
<td>Internet Web-based Randomization System</td>
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STATEMENT OF COMPLIANCE

This study will be conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH) and any applicable national and local laws and regulations (e.g., Title 21 Code of Federal Regulations [21 CFR] Parts 50, 54, 56, 312, and 314). Any episode of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the ICH and Good Clinical Practice (GCP) guidelines and for collecting, recording, and reporting the data accurately and properly. Agreement of each Investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities.

Each Investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in case of a medical emergency.
The Principal Investigator at each center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

**INVESTIGATOR AGREEMENT**

I have read this protocol and agree:

- To conduct the study as outlined herein, in accordance with current Good Clinical Practices (GCPs), the guiding principles of the Declaration of Helsinki and complying with the obligations and requirements of Clinical Investigators and all other requirements listed in 21 CFR Part 312, local regulations, and according to the study procedures provided by Indiana University.
- Not to implement any changes to the protocol without prior agreement from Indiana University and prior review and written approval from the IRB/EC, except as necessary to eliminate an immediate hazard to study patient(s), or for administrative aspects of the study.
- To ensure that all persons assisting me with the study are adequately informed about their study-related duties as desc ribed in the protocol.
- To completely inform all patients in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with GCP and regulatory authority requirements.
- That I will be responsible for maintaining each patient’s consent form in the study file and provide each patient with a signed copy of the consent form.

Investigator Name and Title: _____________________________________________

Institution Address: ___________________________________________________

Signature: ___________________________ Date: __________

**PROTOCOL SUMMARY**

Title: B-lines Lung Ultrasound Guided ED Management of Acute Heart Failure (BLUSHED - AHF)

Précis: Of the one million admissions for AHF in the US, approximately 80% are initially managed in the ED. Outcomes from AHF are poor: nearly 25% are rehospitalized within 30 days of discharge. The evidence base to treat AHF is limited. In fact, there are no pharmacologic therapies with Class I, Level A guideline recommendations. The acute
The treatment of patients today is largely the same as 40 years ago. This proposal aims to build the evidence base for ED AHF care.

Using a multi-center, randomized controlled design, this pilot study will test whether a strategy of care—lung ultrasound (LUS) guided protocol—driven AHF therapy—outperforms usual care at reducing congestion in the ED setting.

**Objectives:**

1. To determine whether a strategy of care—early LUS guided, protocol-driven ED AHF therapy—leads to more rapid resolution of congestion.
2. To demonstrate feasibility of recruitment and compliance with study protocol to inform future study design and enrollment projections.

**Endpoint:**

B-lines ≤ 15 at the conclusion of ED AHF management or maximum of 6 hours after enrollment, whichever comes first.

**Population:**

Emergency department (ED) AHF patients. All patients who meet inclusion and no exclusion criteria will be enrolled within 3 hours of presentation.

**Phase:**

2

**Number of Sites enrolling participants:**

Three sites (4 total hospitals). Projected sample size, n=130.

**Description of Study Agent:**

Strategy of Care: LUS guided protocol—driven ED AHF care vs. usual care.

**Study Duration:**

2 years. There will be three months of startup, and three months of study conclusion work. Enrollment will occur over 18 months, which equals 7.2 patients/month. With 4 sites (2 at IU, 1 at Detroit, and 1 at Vanderbilt), this equals 1.8 patients/month.

**Participant Duration:**

90 days post discharge

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**SCHEMATIC OF STUDY DESIGN**

*whichever comes first

^only if part of standard of care. Only NT pro and hs TnT will be drawn outside of standard of care

**1 KEY ROLES**
Our team of investigators is uniquely qualified to successfully complete this study. We leverage complementary experience and expertise, in particular, early (ED) enrollment, lung ultrasound, congestion management, and clinical trials. Most importantly, we have worked close together for nearly 10 years.1-24

**Peter S. Pang MD (PI)** is an Associate Professor in Emergency Medicine at the Indiana University School of Medicine (IU SOM).

**Christopher O’Connor MD** is the CEO of the Heart and Vascular Institute at INOVA in Virginia. He will serve as a consultant and the principal advisor.

**Vicki Noble MD** (Case Western Reserve University) is an Associate Professor and international ultrasound expert. She will head the Core Lab and function as the independent, blinded, image reviewer.

**Frances Russell MD** is the Director of the Division of Ultrasound and Directs the US Fellowship in the Department of Emergency Medicine at IU SOM. She will lead the study operations related to LUS image acquisition at IU SOM.

**Changyu Shen PhD,** from the Smith Center for Outcomes Research in Cardiology at the Beth Israel Deaconess Medical Center will lead the Data Core at IU.

**Sean Collins MD** (Vanderbilt University), Vice-Chair of Research, will serve as the PI at Vanderbilt.

**Robinson Ferre MD** is an Assistant Professor of Emergency Medicine at Vanderbilt University and Director of the Division of Emergency Ultrasound and Associate Program Director of the emergency ultrasound fellowship. He will lead the study operations related to LUS image acquisition at Vanderbilt.

**Phillip Levy MD** is a Professor of Emergency Medicine at Wayne State University. He will be the Site PI at Detroit Receiving Hospital.

**Rob Ehrman MD** is an Assistant Professor of Emergency Medicine and Assistant Director of Emergency Ultrasound at Detroit Receiving Hospital. He will lead the study operations related to LUS image acquisition at Detroit.

### 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

#### 2.1 BACKGROUND INFORMATION

Over one million hospitalizations for AHF occur every year in the US. Within 30 days after hospitalization, over 25% of AHF patients will be admitted to the hospital, and up to 67% of patients will be hospitalized and 36% will be dead.25-

26 WORLDWIDE, THE cost of AHF exceeds $100 billion annually.27 For patients aged 65 years and older, AHF is the most common and most expensive reason for hospitalization.28 Despite major advances in the treatment of AHF, considerable less progress has been seen in AHF.29-31 The emergency department (ED) initiates diagnosis and management for the vast majority of AHF patients. Nearly 80% of all admissions originate from the ED. Delays in diagnosis, misdiagnosis, and delayed or improper treatment are costly, and associated with greater morbidity and mortality.32,33 One of the most expensive decisions in healthcare is the routine use of imaging studies, particularly chest X-rays.34 In fact, guidelines state: “the treatment of AHF remains largely opinion-based with little good evidence to guide therapy.”35 Consensus statements from the American Heart Association as well as working groups from the NHLBI on EDAHF management further corroborate this lack of evidence: “the evidence base on which this foundation of acute care is built is astonishingly thin.”36,12 Thereremainsacritical unmet need for evidence-based EDAHF management.

Congestion is the primary reason why AHF patients present to the ED seeking medical care.36-40 Congestion is manifest by signs and symptoms of heart failure (HF) — for example, dyspnea, orthopnea, edema, and weight gain. Yethowto best assess, grade, and manage congestion is not well established.39,41 Only recently have heptosing of IV loop diuretics been studied; however, patients were enrolled up to 24 hours after admission.
2.2 RATIONALE

Limitations of Current AHF Therapy

There are recurrent limitations of evidence in therapeutic guidelines for AHF, highlighting the unmet need. In fact, therapeutic recommendations from the ACCF/AHA begin with hospital-based management, highlighting the absence of ED-based evidence. The last ED-based guidelines were published in 2007 and have yet to be updated. Wargu et al. acknowledge that lack of evidence leads to tremendous variation in ED care. Combined, this contributes to worse outcomes.

Targeting Congestion in AHF

Freedom from congestion is associated with improved outcomes, yet many patients leave the hospital inadequately decongested. In fact, many patients leave the hospital without adequate discharge assessment of congestion. We argue that many ED AHF patients are poorly assessed prior to hospitalization. The absence of robust, reliable methods to assess congestion is a primary reason why it is not assessed. A recent consensus statement published in 2010 highlights this fact: “...no method to assess congestion prior to discharge has been validated.” While physical examination is currently the cornerstone of congestion assessment, it lacks sensitivity and inter-rater reliability. The ED is the beginning of AHF management for >75% of admitted patients; delays in diagnosis, misdiagnosis, and resultant delays in management are associated with greater morbidity and mortality.

Lung Ultrasound

For years, the lungs have been considered “off-limits” to ultrasound: with aerated lungs, the ultrasound beam is reflected and scattered due to acoustic mismatch. However, in the setting of pulmonary congestion, extravascular lung water (EVLW) can be directly visualized and quantitated. Lung ultrasound measurement of B-lines are an objective, semi-quantitative measure of extravascular lung water (EVLW). B-lines are well-defined, vertical echogenic lines originating from water-thickened interlobular septa. They are a marker of congestion. Lung ultrasound improves diagnostic accuracy and is highly reproducible. Intra and interobserver variability of B-line capture and summary have been reported as low as 5.1% and 7.4%, respectively. In a recent meta-analysis, LUS was the best test to affirm the diagnosis of AHF, more than natriuretic peptide (NP) (likelihood ratio positive for the diagnosis of AHF by LUS was 7.4 (95% CI 4.2 - 12.8) and LR negative 0.16, (95% CI 0.05 - 0.51)). This may reflect the additional value of LUS when patients have chronically elevated NP levels. Recent guidelines and consensus statements also support the use of LUS for diagnosis.

Figure 1: LUS B Lines

Lung ultrasound measurement of B-lines are an objective, semi-quantitative measure of extravascular lung water (EVLW). B-lines are well-defined, vertical echogenic lines originating from water-thickened interlobular septa. They are a marker of congestion.
Importantly, B-linelines are a dynamic marker. In dialysis patients, B-linelines decrease markedly pre/post dialysis. However, persistence of B-linelines pre-discharge identifies patients at higher risk for worse outcomes. Finally, serial measurement of B-linelines is a useful tool to monitor progression. In AHF patients, B-linelines generally decrease throughout hospitalization. However, persistence of B-linelines pre-discharge identifies patients at higher risk for worse outcomes. B-linelines even outperformed BNP as a prognostic marker. Serial measurement of B-linelines are both easy to learn and perform. LUS is also a low-cost, non-invasive method of echocardiography that does not involve radiation. Computerized diagnostic aids have already been piloted with excellent results, demonstrating the ease of B-linelines scoring. Handheld machines perform as well as a standard ECHO platform or US machines. The ease of LUS will facilitate its generalizability and dissemination. Non-physicians may be future users of bedside LUS assessment, further supporting its generalizability.

**Prior Studies**

Sonographic evidence of pulmonary congestion is associated with worse outcomes.

We performed a single-center pilot study of 44 patients who presented to the ED with dyspnea, evidence of B-linelines by LUS, and were admitted for AHF. Patients underwent LUS imaging during the ED (T0), within 24 hours (T1) and at discharge (Td). Vital status was determined by phone follow-up within 90 days. Using a prespecified cutoff of 15 B-linelines as a marker of persistent pulmonary congestion, 50% of patients had evidence of EVLW at Td. The 28-sector scoring method was utilized. The average number of B-linelines at T0 was 78±47 with a statistically significant reduction at T1 (44±33, p<.001) and Td (26±26, p<.05). (See Figure 2) Thirty-two patients (73%) were successfully contacted for follow-up. During the follow-up period (median: 58 days, interquartile range: 44-82 days), 15 events occurred: 2 deaths and 12 all-cause rehospitalizations. In the subset of patients who experienced events during follow-up, 93% were discharged with persistent presence of pulmonary congestion (≥15 B-linelines) as measured by LUS.

Another pilot study of patients (n=100) admitted to a cardiology ward for shortness of breath and clinical concern for AHF demonstrated a statistically significant reduction in B-linelines at discharge (20+/ -23) vs. admission (48+/ -48, p<.0001). At 6-month follow-up, patients with ≥ 15 B-linelines at discharge were significantly more likely to be hospitalized (HR 11.7 (95% CI 1.3 - 106.6) (See Figure 3). In 27% of patients with >30 B-linelines, no rales were reported by auscultation.

Additional work performed by one of our study team members, Vicki Noble, demonstrated a strong correlation between LUS B-linelines and patients undergoing dialysis. This proof of concept supports B-linelines as responsive to the removal of fluid. Coiro et al. recently published a study of LUS performed throughout hospitalization, demonstrating the prognostic significance of residuum congestion, as measured by B-linelines.
Patients with $\geq 30$ B lines had significantly worse combined outcome of all-cause mortality and HF re-hospitalizations at 90 days. Importantly, these pilot studies also demonstrate the feasibility of performing LUS at the time of presentation and during hospitalization. What has not been tested however, is the use of LUS to guide therapy.

### 2.3 POTENTIAL RISKS AND BENEFITS

#### 2.3.1 KNOWN POTENTIAL RISKS

**Overview.** Current ED AHF treatment involves the use of non-invasive ventilation (NIV), IV loop diuretics, and IV, SL, or topical vasodilators. Each of these are highlighted in guidelines. However, the level of evidence supporting these treatments is relatively weak, with the strongest evidences supporting the use of IV loop diuretics. The evidence is seven weaker for ED AHF treatment; for example, the AHA/ACC guidelines begin with hospitalization, highlighting the lack of evidence for ED AHF care. Although the evidence is weak, these medications are the current standard of care for AHF. In patients receiving strategy -of-care, only therapies currently utilized will be employed. There are no novel therapies or unapproved treatments.

**Common Risks.** The greatest risks are not necessarily different than those already associated with these therapies. However, the risks may not be increased due to use of these treatments in a guided protocol strategy. For IV loop diuretics, commonly encountered risks include potential acute kidney injury (AKI) and overdiuresis leading to hypovolemia. Electrolyte abnormalities may also occur. Per routine standard of care at each of the sites, electrolytes are routinely checked during the initial 24-48 hours of treatment. These will be recorded. However, should no further electrolytes be measured after admission, a pre-discharge lab draw will be performed. While AKI may occur, more recent data suggests that there is no increase in risk of AKI associated with the use of these medications. For NIV, the greatest risk is hypotension. All patients will have IV access for fluids, if needed. Of note, the ESC guidelines allow for the potential use of IV nitrates in patients with SBP > 110 mmHg and only recommend avoiding them if the SBP is < 110 mmHg. Another common side effect is headache, which will be treated with Tylenol or other non-narcotic analgesic medication. Use of NIV is both safe and effective. Greatest risks are those of aspiration in those with altered mental status. However, emergency physicians are well versed in the use of NIV as well. Endotracheal intubation is not applicable to the short-term use of NIV.

An unknown risk is whether our treatment strategy is associated with myocardial injury. Thus, we will measure hsTnT at both baseline and pre-discharge to ascertain the incidence of myocardial injury. Such measurements of hsTnT and potential electrolyte abnormalities, eGFR, and pre-specified NTproBNP and Hgb/Hct will require additional blood draws, and these will be limited in volume. No more than 40 cc total will be drawn for study purposes. While there are no known serious health risks related to the additional blood draw, there is the potential risk of pain, bruising, and rarely infection. Blood will be drawn by experienced technicians or research staff and whenever possible it will be obtained at a time when blood is being obtained for other tests that were reordered.

#### 2.3.2 KNOWN POTENTIAL BENEFITS

Patients enrolled in this study who are receiving the strategy -of-care are also expected to receive benefits such as decreased mortality, fewer frequent hospitalizations related to HF, or feeling better faster, or having less myocardial injury.
AHF patients, if this study demonstrates sufficient safety to test in a future efficacy study, which if positive will show that the ED AHF strategy -of-care has beneficial clinical outcomes. If the study shows that a LUS guided ED AHF strategy—of-care is not safe with the current study design, future patients may be spared the cost of ineffective ED AHF management, and spared the potential for any possible side effects.

### 3 OBJECTIVES AND PURPOSE

**Objectives:**

1. To determine whether a strategy of care—early LUS guided, protocol-driven ED AHF therapy—leads to more rapid resolution of congestion.

2. To demonstrate feasibility of recruitment and compliance with study protocol to inform future study design and enrollment projections

**Purpose:**

This pilot trial is designed to provide the necessary and sufficient information for a larger, definitive trial. 

**Our overarching hypothesis:** A protocol-driven ED AHF strategy—of-care, guided by lung ultrasound (LUS), will lead to improved 30 and 90-day outcomes. Importantly, this strategy—of-care will utilize only currently available therapies—non-invasive ventilation, vasodilators (sublingual, topical, and/or IV), and IV loop diuretics. Successful completion of four specific aims will provide the necessary and sufficient information to determine whether a LUS guided ED strategy leads to more rapid and sustained decongestion. Subsequent multi-center, randomized, simple, strategy—of-care trial, will test whether LUS guided, protocol-driven ED AHF management reduces 30 and 90-day post-discharge days alive and out of hospital (DAOOH).

We focus on a subset of AHF patients. If successful, we may expand the patient population in future studies. However, the following critical issues need to be addressed prior to initiation of a large, simple, efficacy study: does ED AHF management, guided by LUS, lead to rapid and sustained decongestion and mortality?

Although this pilot study focuses solely on ED management, we will assess patients throughout hospitalization, carefully following management to inform subsequent trial design. To minimize heterogeneity of treatment, we will exclude patients in cardiogenic shock or hypertensive emergency. This project will generate new, critically important knowledge about the ED phase of AHF management.

### 4 STUDY DESIGN AND ENDPOINTS

#### 4.1 DESCRIPTION OF THE STUDY DESIGN

A multi-center, prospective, randomized, controlled, unblinded strategy—of-care trial. All potential ED patients will receive an initial LUS scan. Performing LUS is within the standard of care and will be done at no cost to patients. It is not frequently used however, either for diagnosis, prognosis, or to guide clinical therapy. However, treating clinicians will be blinded to the results of LUS and the diagnosis of the usual care arm. If clinicians choose to perform their own LUS, those patients will not be excluded. Patients who provide written informed consent and meet all inclusion and no exclusion criteria will be randomized: 1) to our LUS guided strategy—of-care; 2) to usual care. While a further LUS guided intervention will occur for usual care patients, similar to our LUS guided arm, serial LUS assessments will occur throughout hospitalization as well as pre-specification. If biomarkers and physical exam. For patients randomized to the strategy—of-care arm, the LUS guided protocol will be initiated and continued until there is a decrease in B lines to ≤ 15 or 6 hours of care has been delivered or the patient has left the ED, whichever comes first. Trained research personnel will acquire LUS images. All images will be stored and overread by an independent expert ultrasonographer blinded to treatment arm.
Safety of patients are paramount. If a potential lifethreatening etiology is identified, the clinical team will be made aware immediately, irrespective of randomization arm. These occurrences will be recorded in the eCRF. While this will be a rare event, we will establish that an additional patient will be accrued into the study and an additional modified intent-to-treat population for analysis will be performed, excluding these patients where a life-threatening etiology was identified (i.e., pericardial tamponade).

For patients who do NOT meet eligibility criteria, the results of their LUS will be provided to the clinical team as requested, as these patients are no longer at risk for contamination of the usual care arm.

4.2.1 PRIMARY ENDPOINT

B-lines ≤ 15 at the conclusion of ED AHF management (i.e., patient has left the ED) or maximum of 6 hours after enrollment, whichever comes first.

4.2.2 EXPLORATORY ENDPOINTS

The following table lists the exploratory endpoints:

<table>
<thead>
<tr>
<th>Table 3: Exploratory Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DAOOH through 30 and 90 days post-discharge</td>
</tr>
<tr>
<td>Change in biomarkers from presentation to pre-discharge</td>
</tr>
<tr>
<td>Time to reach B-lines &lt;15</td>
</tr>
<tr>
<td>Composite of 30-day all-cause mortality, cardiovascular (CV) rehospitalizations, and CV emergency department (ED) revisits. CV endpoints are defined according to the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events.87</td>
</tr>
<tr>
<td>Also for same endpoint, but through 90 days</td>
</tr>
<tr>
<td>Change in physical exam findings and body weight from presentation to pre-discharge</td>
</tr>
<tr>
<td>Description of hospital based AHF treatment</td>
</tr>
</tbody>
</table>

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1) Age ≥ 21 years
2) Presents with shortness of breath at rest or with minimal exertion
3) Clinical diagnosis of AHF and presence of >15 total bilateral B-lines distributed in at least 4 zones on initial LUS
4) History of chronic HF and any one of the following:
   i. Chest radiograph consistent with AHF
   ii. Jugular venous distension
   iii. Pulmonary rales on auscultation
   iv. Lower extremity edema
5.2 PARTICIPANT EXCLUSION CRITERIA

1) Chronic renal dysfunction, including ESRD or eGFR < 45 ml/min/1.73m².

2) Shock of any kind. Any requirement for vasopressors or inotropes.

3) SBP < 100 or > 175 mmHg

4) Need for immediate intubation

5) Acute Coronary Syndrome OR new ST-segment elevation/depression on EKG. (Troponin release outside of ACS is allowed)

6) Fever > 101.5°F

7) End stage HF: transplant list, ventricular assist device

8) Anemia requiring transfusion

9) Known interstitial lung disease

10) Suspected acute lung injury or respiratory distress syndrome (ARDS)

11) Pregnant or recently pregnant within the last 6 months

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Each site will have a lead PI and US Director, along with a dedicated study team. This study team, comprised of research assistants and coordinators, will perform both electronic screening (via tracking boards) and maintain a continuous physical presence in the ED to identify patients. All sites currently screen patients at minimum 16 hours each day, 5 days per week. Additionally, Detroit has a 24/7 program, Vanderbilt does this 6 days a week, and Indianapolis has 6 hours of coverage on the weekends. These methods have been utilized with success in previous trials. Standard computerized internet-based screening logs will be maintained to identify ED AHF patients admitted to the hospital and record screen failures. All patients with a final diagnosis of AHF at the time of hospital discharge will be considered to have AHF.

As we aim to design a pragmatic, ED-based study, our inclusion/exclusion criteria are relatively broad compared to other therapeutic clinical trials.

Screen Failures:

Patients who sign an informed consent but who are not randomized will be considered Screen Failures. Only data for randomized patients will be entered into the CRF. Serious adverse events should be reported for these patients from the time the ICF is signed through the time the patient is declared a screen failure. One expected reason for screen failure will be the absence of > 15 B-lines at baseline.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

In accordance with the guiding principles of the Declaration of Helsinki, any patient is free to withdraw from participating in the study at any time and for whatever reason, specified or unspecified, and without prejudice. Investigators should attempt to determine the cause of withdrawal and, if desired by the patient, make it possible for the patient to continue participating in the study. The extent of a patient's withdrawal from the study (i.e. withdrawal from further study treatment, withdrawal from any further contact, etc.) should be documented. Every effort should be taken to follow all randomized patients, to the extent that the patient will allow, for the full follow-up period.

Investigators may discontinue study treatment for any other reasons concerning the health or well-being of the patient.
The reason for and date of study discontinuation and the reason for and date of withdrawal from the study must be recorded on the CRF. If study is discontinued because of an adverse event or a clinically significant abnormal laboratory test result, evaluations will continue until the event has resolved or stabilized or until a determination of a cause unrelated to the study procedure is made. The specific event or laboratory finding(s) must be documented. All evaluations should be performed, according to the protocol.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

The Full Analysis Set (FAS) will include all randomized patients. In accordance with the intent-to-treat principle, patients will be analyzed by the group to which they were randomized. Misrandomized patients (patients randomized in error who did not receive any study intervention) will be excluded. Analyses in the FAS will constitute the main efficacy results for the primary and secondary study efficacy endpoints.

The Per Protocol Set (PPS) will be a subset of the FAS and will exclude patients with major protocol violations. The major protocol violations that will result in exclusion from the PPS will be identified prior to unblinding the treatment assignments for final analysis. Patients will be analyzed by the treatment group to which they were randomized. Results of analyses in this analysis population will support the primary efficacy analyses in the FAS.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The study is overseen by a DSMB. They may terminate the study at any time if the safety of patients is at jeopardy.

6 STUDY AGENT

6.1 STUDY AGENTS (S) AND CONTROL DESCRIPTION

This study will test a strategy of care vs. usual care for ED AHF management. Only therapies already in use will be applied. For example, NIV, IV loop diuretics, and nitrovasodilators. The usual care arm will also follow the treatment protocol, unless the clinician explicitly states no further treatment is warranted based on their clinical assessment to better reflect real-world conditions. No drugs or therapies that are not approved by the FDA will be allowed.

6.1.1 DOSING & DOSE ESCALATION

The algorithm below outlines the treatment protocol.
• All enrolled patients should receive IV furosemide per the protocol box.
  o IF patients already received furosemide prior to the time of enrollment, BRANCH point.
    ▪ Patients in usual care arm will NOT receive any further diuretic.
    ▪ Patients in LUS arm will receive further diuretic (equal to 2x oral dose). For example, if the patient usually takes 80 mg BID at home, but then already received 40 mg at arrival to the ED, if in the LUS arm, would receive an extra 120 mg. (200 is the maximum single time dose.)
• Clinical assessments should be recorded irrespective of treatment arm. However, the initial ED LUS assessment will be considered Time 0.
*IMPORTANT – the clinical assessment alone arm will ALSO have LUS performed – however, the results will NOT be shared with the clinical caregiving team.*

** ALL enrolled patients will be assessed at least twice during their ED stay. First assessment will occur within 2 - 4 hours of first TREATMENT. Assessments outside this window are NOT allowed for study purposes unless at the discretion of the investigator. The second assessment will occur between 2 - 4 hours after the first OR prior to discharge. If the pre-discharge assessment is missed in the ER, this should occur as soon as possible after arrival to the hospital floor.

NOTE: The maximum dose allowed at any one time of IV Lasix is 200mg IV.

NOTE: For additi onal IV loop diuretic doses, the options under Restart Algorithm are three options. Clinical/Research team may choose one of the three loop diuretic dose options.

NOTE: For both arms: After each reassessment, the clinical physician will be asked:

1. “In your clinical opinion, is the patient still volume overloaded?” (Yes, No, Not sure)
2. If Yes, then the following question will be asked: “Do you think the patient warrants additional treatment now?”
3. If Yes, then FOR THE CLINICAL ASSESSMENT ARM ONLY: treatment will occur **per the algorithm.** (Patients in the LUS intervention arm will ONLY receive further therapy guided by LUS)

NOTE: The protocol is not optional. Of course, patient safety comes first, similar to all other interventional trials. However, similar to other interventional studies, once randomized, the study protocol should continue forward. If, in the opinion of the investigator, continuing treatment is potentially unsafe (i.e. SBP has decreased significantly, very brisk diuresis), up titration per protocol may be held.

The protocol continues until 6 hours after randomization. Even if the patient is on the floor and under the care of the inpatient team, the protocol should not be continued on the hospital floor, this is allowed and should be marked on the case report form.

### 6.1.2 DURATION OF THERAPY

Both arms will continue until 6 hours after randomization. 6 hours was chosen to avoid confounding by patients with overly long ED LOS. At minimum, patients should receive at least one round of treatment. The protocol continues even if patients reach the floor. However, if in the opinion of the investigator, the protocol should not be continued on the hospital floor, this is allowed and should be marked on the case report form.

### 7 STUDY PROCEDURES AND SCHEDULE

#### 7.1 STUDY PROCEDURES/EVALUATIONS

#### 7.1.1 STUDY SPECIFIC PROCEDURES

The table below in section 7.3.7 highlights study specific procedures. Only patients who sign written informed consent will undergo these specific procedures.
 Except for the ED phase of management, there will be no other change to standard of care procedures for either treatment arm. Patients will continue to be assessed however, during hospitalization.

### 7.2 LABORATORY PROCEDURES/EVALUATIONS

#### 7.2.1 CLINICAL LABORATORY EVALUATIONS

Lab testing will be analyzed by the clinical lab at each respective institution for baseline chemistry and hemoglobin/hematocrit values. This reflects our pragmatic approach. If routine labs are performed clinically within 6 hours of the follow-up time-point, these results will be used for study purposes (Table 2). If routine labs are not drawn, the closest clinical lab draw will be recorded in the CRF unless already recorded (i.e., the baseline value). NO labs, other than NTproBNP and hsTnT will be drawn for study purposes. Samples will be stored and shipped to Indiana University at the Clinical and Translational Sciences Laboratory. At quarterly intervals, samples will be analyzed in our core lab, with expertise in clinical lab sampling.

All clinical laboratory test results outside of the reference range will be interpreted in the context of the patient's underlying disease state by the Investigator using the following categories:

- abnormal but not clinically - significant worsening
- abnormal and clinically - significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) compared with the baseline result will be recorded on the CRF as an adverse event and monitored. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing as needed) that results in the temporary or permanent cessation of treatment, requires medical treatment or further diagnostic work-up. The AE and SAE reporting period extends to day 5 of hospitalization or discharge, whichever comes first, unless otherwise specified.

A local laboratory will be utilized to analyze screening entry criteria.

#### 7.2.2 OTHER ASSAYS OR PROCEDURES

NT-proBNP and hsTnT levels will be analyzed centrally. Roche Diagnostics will provide in-kind support for the cost of analytical testing and reagent support.

#### 7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

All human body fluids should be handled as potentially infectious. Personal protective equipment should be used. If any blood is collected using an indwelling catheter at least 0.5 mL discard sample will be taken if the catheter was flushed with saline.

2 aliquots per sample type per collection = 6 total aliquots

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Tube Type</th>
<th>Blood Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 = 0 hour (Baseline)</td>
<td>SerumSeparator</td>
<td>Onetube, ~4cc</td>
</tr>
<tr>
<td></td>
<td>Lithium Heparin</td>
<td>Onetube, ~4cc</td>
</tr>
<tr>
<td></td>
<td>EDTA Plasma</td>
<td>Onetube, ~4cc</td>
</tr>
<tr>
<td></td>
<td>SerumSeparator</td>
<td>Onetube, ~4cc</td>
</tr>
</tbody>
</table>
T1 = Day 7 or discharge +/ - 24 hours

<table>
<thead>
<tr>
<th></th>
<th>Lithium Heparin</th>
<th>EDTA Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onetube, ~4cc</td>
<td></td>
<td>Onetube, ~4cc</td>
</tr>
</tbody>
</table>

Samples will be collected in the following order:

1. Serum separator
2. Lithium heparin
3. EDTA plasma

Every attempt to collect both samples should be made.

Specimens must be processed within 3 hours of collection and no later than 4 hours. This includes collection, centrifuge, aliquot, and then frozen. Samples should be held at 4 degrees Celsius until processed.

Standard venipuncture techniques or other standard blood collection methods will be used. These must be in accordance with institutional standards, policies, guidelines, recommendations, and requirements.

After collection, please use the following instructions for guidance. If there is doubt, the tube manufacturer instructions are the final arbiter for any disputes.

**Serum:** After collection, let sit at room temperature for ~30 minutes to allow clotting to occur. Then centrifuge at 1000-1300 g for 10-15 minutes at room temperature.

**Lithium Heparin plasma:** After collection, invert tube gently 10 times to ensure mixing with anti-coagulant. Then centrifuge at 1000-1300 g for 10-15 minutes at room temperature.

**EDTA:** After collection, invert tube gently 10 times to ensure mixing with anti-coagulant. Then centrifuge at 1000-1300 g for 10-15 minutes at room temperature.

All tubes should be removed from centrifuge immediately upon completion and when safe to do so. Remove at least 0.5 cc of supernatant for each aliquot, with 2 aliquots per tube. DO NOT MIX or pool supernatants together.

Each aliquot must be stored in an appropriate cryovial, for storage at -20 degrees Celsius or colder. Cryovials are pre-labeled without PHI.

Freezers must have temperature logs available for review.

### 7.2.4 SPECIMEN SHIPPING

Frozen biomarkers specimens will be batch shipped on a quarterly enrollment basis on Dry Ice. A specimen shipping form will accompany all shipments with a copy kept at the site. All samples should be stored at -20 degrees Celsius until the sample is shipped. Whole blood will be collected, processed (centrifuged locally) and stored appropriately for shipment to Indiana University (IU) for central processing.

All personnel responsible for shipping of specimens are certified by the respective institutions. IU will provide the minimum required procedures. Shipping procedures are defined by the appropriate CTSL standard operating procedures. Shipping services, if required, will include documentation, QC, manifest creation, and dry ice (if required). Detailed shipping information will be sent to each site prior to shipment.

### 7.3 STUDY SCHEDULE

#### 7.3.1 SCREENING
A signed and dated informed consent form will be obtained before any study-specific screening procedures are performed. Results of evaluations obtained as part of routine medical care, which are performed prior to obtaining informed consent, may be used in place of the protocol-specified evaluations. Patients will acknowledge and agree to the use of this information for the study by giving informed consent.

At the baseline visit, patients will be assigned by the Internet Web-based Randomization System (IWRS) a unique permanent identification number referred to as the patient identification number such that all randomized patients from each center are given consecutive identification numbers by the IWRS in successive order of inclusion. We will utilize the REDCap randomization module. (NOTE: thus each patient will have two ID’s – 1) generated by IWRS and 2) blood specimen label)

Prospective study patients will have presented to the hospital for urgent therapy for AHF. Potential patients will be identified either en route to or upon arriving at the ED/hospital. Routine assessments associated with usual patient care may be used for the purposes of screening and may be completed in any order. Study specific procedures must be completed only after informed consent is obtained.

Randomization will occur within three hours of patient’s arrival to a room within the ED where they can be seen by a physician or the first time AHF treatment is given. Waiting room time does not count against these three hours.

The following procedures will be performed prior to or during screening:

- Obtain written informed consent (must be performed as the first study-specific procedure)
- Review of prior medical history
- Review of prior and concomitant medications
- Physical examination (including height and weight when reasonably possible)
- Vital signs measurements (include systolic and diastolic blood pressures, heart rate, body temperature, oxygen saturation, reading and respiratory rate)
- 12-Lead Electrocardiogram
- Chest X-Ray (this is not a requirement however, for inclusion)
- Blood collection for local laboratory tests, including BNP or NT-proBNP, and pregnancy test if applicable.
- Inquiry about Adverse events

7.3.2 Enrollment/Baseline

Patients who continue to fulfill all of the inclusion/exclusion criteria will be randomized no later than 3 hours after the first recorded timestamp when the patient placed in a room to be seen by a provider. Waiting room time does not count. Randomization will occur via the central IWRS system.

7.3.3 Follow-up & Final Study Visit

Patients will be followed for a maximum of 90 days post-discharge. There will be no further in-person visits once discharged. Patients will be called however at 30 and 90 days post-discharge (+) 30 business days or at the discretion of the local site PI to assess vital status and re-hospitalizations or ED visits.

7.3.7 Schedule of Events Table
<table>
<thead>
<tr>
<th>Schedule of Events</th>
<th>Screening</th>
<th>Day 1 T00</th>
<th>Day 1 T02-04</th>
<th>Day 1 T06</th>
<th>Day 2-6 T24-D6</th>
<th>Day 7 or D/C*</th>
<th>30 &amp; 90 day follow up</th>
<th>Quarterly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent (I/E)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Medical History</td>
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<tr>
<td>Medication history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Assessment*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight, height, Vital Signs</td>
<td>ED SOC</td>
<td>VS only</td>
<td>VS only</td>
<td>VS only</td>
<td>BW/VS only</td>
<td>BW/VS only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labs: Electrolytes, hematology, NP, eGFR, Troponin</td>
<td>ED SOC</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>NT-proBNP / hsTroponin (for central lab processing)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>ED SOC</td>
<td></td>
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<tr>
<td>CXR</td>
<td>ED SOC</td>
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<td></td>
</tr>
<tr>
<td>LUS B-lines 8 zone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>(LUS T00)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LUS Guided AHF Management or Usual Care</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lab draw: eGFR, Hgb/Hct*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Prep and Storage of Samples</td>
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<td></td>
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<td></td>
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<tr>
<td>eCRF/data collection/verification</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SOC = standard of care, ED = Emergency Department, I/E = inclusion, exclusion, CV = cardiovascular, LUS = lung ultrasound, BW = bodyweight, NP = natriuretic peptide. If collected as part of standard of care, will use that result. The last collected result will be used if not drawn on or close to discharge. *Day 7 or discharge, whichever comes first. #As documented by clinician during inpatient stay or perform for ED phase.

Further details regarding timing of assessments: [NOTE: given clinical circumstances (i.e. left the ER for a test, discussion with consultant, etc) – the site PI has final discretion to continue to image a patient before or after the allotted window. This time MUST be recorded in the eCRF]

<table>
<thead>
<tr>
<th>Assessment of AE/SAE’s</th>
<th></th>
<th></th>
<th></th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone follow-up Vital Status</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Batch shipment of samples</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Subject payment</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Further details regarding timing of assessments: [NOTE: given clinical circumstances (i.e. left the ER for a test, discussion with consultant, etc) – the site PI has final discretion to continue to image a patient before or after the allotted window. This time MUST be recorded in the eCRF]

- T00: Initial LUS scan (in ED for screening and eligibility)
- T02: 2-4 hours after initial treatment (in ED) (+/- 30 minutes)
- T06: 2-4 hours after T02 or pre-ED discharge, whichever comes first (+/- 60 minutes)
- HD2: 24 hours after initial scan (Day 2) (+/- 6 hours)
- HD3: 48 hours after initial scan (Day 3) (+/- 8 hours)
- HD4: Day 4 (anytime during day)
- HD5: Day 5 (anytime during day)
- HD6: Day 6 (anytime during day)
- HD7: Day 7 (anytime during day)

*NTproBNP/hsTnT Blood draw. This should occur within 6 hours of randomization. Ideally, the blood draw should occur as soon as possible after randomization, preferably within 3 hours.

**For vital signs during hospitalization. The nearest vital sign to the LUS exam will be captured.

^HD = Hospital day

7.5 CONCOMITANT MEDICATIONS

All medications administered within 14 days prior to and during screening will be recorded in the case report form. Medications that are not specifically prohibited are permitted at the Investigator’s discretion.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

No medications, treatments, or procedures are prohibited unless specifically mentioned in the eligibility criteria. Patient safety and well-being are paramount. Any treatment deemed necessary may be utilized at the investigator’s discretion should there be any concern for the patient’s health.

8 ASSESSMENT OF SAFETY
In addition to standard safety monitoring by the sponsor, an independent DSMB will oversee patient safety in the trial. The DSMB will meet as specified in its charter.

8.1 SPECIFICATION OF SAFETY PARAMETERS

Mortality, readmission, and ED visit through 90 days will be assessed for safety as well as efficacy.

Hypotension, defined as a SBP < 100 mmHg, will be assessed as a safety endpoint. **SBP Decrease Safety Margin:** Patients whose SBP decreases to < 100 mmHg at any time (measurement must be repeated twice, 15 minutes apart, unless symptomatic) or who develop evidence of clinical hypotension (i.e., weakness, dizziness, faint, chest discomfort) despite a SBP > 100 mmHg will be immediately assessed and treated as needed, and all further strategy of care interventions will be halted. Patient safety and care is paramount and takes precedence over all other considerations. The clinical team may halt the study at any time. If there are any questions, the PI or designee will make the final decision.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

The Investigator and study staff are responsible for detecting and recording AEs and SAEs during scheduled safety evaluations and whenever such information is brought to their attention. This section of the protocol provides definitions and detailed procedures to be followed. During each visit, the Investigator will question the patient about adverse events using an open question, taking care not to influence the patient’s answers, e.g., “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.”

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution. This includes:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values that fall into an abnormal range based upon the hospital’s laboratory standards, the abnormality was not preexisting prior to enrollment, and the abnormality leads to a new treatment within the AE time frame.

The AE and SAE reporting period extends to the day of hospitalization or discharge, whichever comes first, unless otherwise specified.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE will be classified as an SAE if:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions).
8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The severity of each adverse event must be recorded as one of the choices on the following scale:

- **Mild**: No limitation of usual activities
- **Moderate**: Some limitation of usual activities
- **Severe**: Inability to carry out usual activities

An AE that is assessed as severe should not be confused with a SAE.

8.2.2 RELATIONSHIP TO STUDY AGENT

Each reported AE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, and suspected relationship to study drug (according to the definitions set forth at each IRB). In general, these relationships are categorized as likely, possible, unlikely, and not related. Experience teaches that gray zone instances will arise, and the site coordinators and PIs will be trained to adjudicate possible SAEs in a systematic fashion. To ensure consistency of SAE causality assessments, investigators will apply the following general guideline:

**Yes** - There is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the subject’s clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to study drug or the AE abates or resolves upon discontinuation of study drug.

**No** - Evidence exists that the AE has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to the study drug.

Adjudication of each AE will proceed as follows: First, the coordinator will consult the site PI to review the chart. Next, the PI will contact members of the clinical care team to clarify uncertainty related to inadequate documentation. Third, if the PI is unable to decide for certain if an AE or SAE occurred, he or she will have the option of sending a personal health identifier-stripped, written narrative of the event to the other site PIs who will vote up or down as to whether the event constituted an AE or SAE.

8.2.3 EXPECTEDNESS

The following signs, symptoms, observations, and events are frequently observed in association with acute heart failure:

- Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, chest pain, fever, hypoxemia, rapid pulse, rapid respiratory rate, dizziness, syncope, altered mental status, confusion, anxiety, generalized weakness, anorexia, nausea, abdominal pain, back pain, early satiety, vomiting, pneumonia, acuterenal failure, skin infection, cancer, surgery not related to treatment of pulmonary embolism, electrocardiography abnormalities (atrial arrhythmias, ventricular dysrhythmias, right bundle branch block, and ST and T wave changes), elevated troponin level, elevatedBNP or NT ProBNP level, high white blood cell count, pulmonary infiltrate, pleural effusion, cardiomegaly, electrolyte imbalances, need for oxygen therapy, need for vasopressor support, need for blood product transfusion, need for mechanical ventilation (invasive or non-invasive), need for physical or occupational therapy, need for skilled nursing facility upon
discharge, need for early follow-up with physician, escalation of heart failure therapy, need for cardiac catheterization or P-line placement, need for sleep study.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All AEs and SAEs will be followed through resolution, stabilization, or until the subject is lost to follow-up.

Theonset and end dates, duration, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the CRF for randomized patients. The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the Investigator, must be recorded as described below.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The study period during which AEs must be reported begins after informed consent is obtained and initiation of study treatment and for 7 days after ending study treatment. Subject’s hospital discharge summaries will be examined at hospital discharge and all non-exempt AEs will be investigated by examining necessary medical records.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be reviewed within 48 hours and all AEs within 7 days of discovery by the Study Monitor (also known as the medical monitor). Any SAE discovery will be reported to the DCC, who will then report to the DSMB, who will be unblinded. If placebo treated patient, standard reporting to the IRB will occur. If active treated patient, and deemed to be related to drug, the SAE will be reported to the DSMB chair within 7 business days by email, fax, or phone of any fatal or life-threatening adverse event that is unexpected.

15 Calendar Day Written Report

The Investigator will also be required to notify the IRB and all participating investigators, in a written Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the strategy of care arm -of carearm

72 hour reporting

For the discovery of an unexpected serious adverse event thought to be related to study drug, the Investigator(s) will notify the Chair of the DSMB by email within 72 hours.

8.5 STUDY HALTING RULES

Please see separate DSMB Charter

8.6 SAFETY OVERSIGHT

Please see separate DSMB Charter

9 CLINICAL MONITORING

Sites will be remotely monitored. Should the need arise for further investigation, an independent monitor will be appointed to visit sites. Each site has extensive clinical trial experience and the expectation for this need is low. Nevertheless, the PI will visit each site at least once per year for meeting with study staff and random surveillance.

10 STATISTICAL CONSIDERATIONS
10.1 STATISTICAL AND ANALYTICAL PLANS

Previous work demonstrates the value of B-lines to improve both diagnosis and prognosis in AHF. Whether targeting B-lines to guide therapy results in improved outcomes is unknown. Prior to examining outcomes however, a key step is required: does LUS guided, protocol-driven treatment result in less B-lines than usual care? In other words, can B-lines be actively targeted as a treatment endpoint?

10.2 STATISTICAL HYPOTHESES

- **Hypothesis 1:** LUS guided patients will have less congestion, defined by LUS B-lines <15, than usual care patients at 6 hours after start of treatment. Other measures of congestion, such as serial LUS during hospitalization, physical exam, NT-proBNP, and hemoglobin/hematocrit levels will be assessed to determine the superiority of LUS.

- **Exploratory Hypothesis:** Strategy-of-care patients will have more days alive and out of hospital (DAOOH) at 30 days.
  - Strategy-of-care patients will have more days alive and out of hospital (DAOOH) at 90 days.

- **Hypothesis 2:** Each site (n=4) will enroll ~2 patients per month for 18 months.

10.3 ANALYSIS DATASETS

The Full Analysis Set (FAS) will include all randomized patients. In accordance with the intent-to-treat principle, patients will be analyzed by the group to which they were randomized. Misrandomized patients (patients randomized in error who did not receive any study intervention) will be excluded. Analyses in the FAS will constitute the main efficacy results for the primary and secondary study endpoints.

The Per Protocol Set (PPS) will be a subset of the FAS and will exclude patients with major protocol violations. The major protocol violation that will result in exclusion from the PPS will be identified prior to unblinding the treatment assignments for final analysis. Patients will be analyzed in the treatment group to which they were randomized. Results of analyses in the PPS will support the primary efficacy analyses in the FAS.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Unless stated otherwise, two-sided p-values < 0.05 will be considered statistically significant, without regard to multiple comparisons. Statistical tables and listings and analyses will be produced using SAS® release 9.1 or later (SAS Institute, Inc., Cary, NC, USA) or other validated statistical software.

10.4.2 BASELINE DESCRIPTIVE STATISTICS

We will tabulate baseline characteristics of the two trial arms for potential imbalance in variables. Continuous variables will be summarized by typical parameters such as mean, standard deviation and range and compared using two-sample T-test (if the normality assumption holds) or Wilcoxon rank-sum test (if the normality assumption does not hold). Normality of distribution will be determined using the Kolmogorov-Smirnov goodness-of-fit test. Categorical data will be summarized by frequency and percentage and analyzed using the Chi-square or Fisher's exact test, as appropriate.

The use of prior and concomitant medications will be summarized. The use and doses of furosemide in equivalents will be summarized by treatment group. Other concomitant medications will be coded using WHODrug and summarized by treatment group according to Anatomic Therapeutic Classification and preferred term.
10.4.3 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The comparison of binary endpoints (B-lines < 15) will be performed using Chi-square or Fishers exact test, as appropriate.

Potential covariates will also be considered in a logistic regression setting to improve precision, which includes baseline co-morbidities, baseline medications (in particular guideline recommended therapies), in-hospital medications, baseline renal function, serum sodium, natriuretic peptide levels, troponin levels, renal function, baseline blood pressure, and discharge medications. Variables such as physical exam, other vital signs, and hemococoncentration may also be included. For NT-proBNP, a percent change greater than 30% and its association with the primary endpoint will be analyzed. This is based on previous work suggesting a 30% change was a key discriminatory threshold for mortality. For hemoconcentration, any increase in value in both hematocrit and hemoglobin during hospitalization will be considered positive. These covariates are known markers of risk and are standard of care assessments for the vast majority of AHF admissions. Covariates with univariately significant association with the outcome will be included together with the treatment indicator in a logistic regression model. Due to limited sample size, we will limit the number of covariates (including treatment indicator) such that there is 10 events per covariate.

10.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

DAOOH: Will be compared using T-test or Wilcoxon rank-sum test, as appropriate.

If the distribution of 30 or 90 days DAOOH is skewed, the T-test may not perform satisfactorily. An alternative approach to evaluate the robustness of the analysis is to use the proportional odds (PO) regression model to compare the two groups and use the Wilcoxon (Mann-Whitney) test to estimate the shift in the distribution of DAOOH by the intervention. The PO regression allows for adjustment of baseline covariates to enhance power.

We will examine the distribution of B-lines measurements for the groups with and without events separately. Both absolute number and relative change will be evaluated. Receiver Operating Characteristic (ROC) curves will be plotted together with the area under the curve (AUC) to calculate the prediction performance of the B-line measurements. Sensitivity, specificity, positive and negative predictive values will be computed using a threshold of B-lines. Confidence intervals of statistical measures will be constructed using the bootstrap method.

For reproducibility analysis, generalized linear mixed-effects models will be fitted to estimate the inter- and intra-observer variability, where both patients and observers are treated as random effects.

Wewill compare parameters used to identify congestion. This will include a comparison between B-lines measurements and other markers, such as physical exam, NT-proBNP, eGFR, and hemoglobin/hematocrit. Bootstrap methods will be used to compare the m-parity with account for correlations between the other markers and B-lines. We will consider two strategies to explore potential multivariate models:

1. Logistic regression models: We will consider three different models. First, we include all markers except B-lines in the model (Model 1). Second, we will explore all main effects models that can be built using B-lines along with the other markers and select the one with the best model fitting characteristic (e.g., Akaika Information Criterion or Bayesian Information Criterion) (Model 2). Third, we will explore all main effects models that can be built using only the other markers (Model 3). These models will allow us to create a discriminating score for the prediction of 30- or 90-day outcomes.
2. **Tree based nonparametric method**: We will employ the classification tree to build a nonparametric prediction model using B-lines measurements and the seven other markers (Model 4). We will build a similar classification tree without the involvement of the B-lines measurements (Model 5).

Models 1-5 will be evaluated using data from the testing set in terms of prediction accuracy. In particular, Models 2 and 3, 4 and 5 will be compared (if there is a difference between models 2 and 3 and between 4 and 5) to understand the net reclassification rate. Statistical inference of the comparison will be performed using the bootstrap method.

### 10.4.5 SAFETY ANALYSES

Hypotensive events will be reported per treatment arm as well as other safety events ascertained during the study. Continuous variables will be summarized by typical parameters such as mean, standard deviation and range, and compared using two-sample T-test (if the normality assumption holds) or Wilcoxon rank-sum test (if the normality assumption does not hold). Normality of distribution will be determined using the Kolmogorov-Smirnov goodness-of-fit test. Categorical data will be summarized by frequency and percentage and analyzed using the Chi-square or Fisher’s exact test, as appropriate.

As all cause mortality and all hospitalizations will already be reported as part of the efficacy exploratory analyses, these will also be highlighted as safety analyses.

### 10.4.6 ADHERENCE AND RETENTION ANALYSES

**Missing data**: We will compare relevant patient characteristics between those who stay in the study and those who drop out to examine whether there are characteristics that discriminate between the two groups. It is possible that the dropout mechanism does not depend on unobserved outcomes (Missing At Random, or MAR), where no bias will be introduced by ignoring the missing -data mechanism. We can simply use all observed outcomes for the analysis. Under circumstances where power loss is of concern, we will use multiple imputation procedure to make use of all relevant observed variables to enhance power. The SAS procedure MI and MIANALYZE will be used for implementation of this procedure.

In case the dropouts are Missing Not At Random (MNAR), which means the likelihood of drop-out depends on unobserved outcomes, we will make various assumptions regarding the missing -data process. With these assumptions, we will fit proper models, either in the form of selection model, pattern mixture model, or latent variable model to account for the missing -data process. A sensitivity analysis will be conducted to compare the results based on different assumptions and models and assess the robustness of the inference.

### 10.4.7 PLANNED INTERIM ANALYSES

- Per the DSMB charter, there is a single, formal interim analysis planned after 50% of patients are accrued. No formal stopping rules have been established, given the small sample size. Rather, the DSMB will issue recommendations on halting the trial early, only for safety reasons, based on the totality of data reviewed.

### 10.5 SAMPLE SIZE

Our preliminary data suggest that 25% of patients in the usual care arm will have < 15 B-lines at the conclusion of AHF management. With 59 patients in each arm, we will have 81% power to detect an effect size of 2 (i.e. 25% in the usual care versus 50% in the strategy care), where the type I error rate is controlled at 0.05 (two-sided). Considering a conservative 10% drop-out rate, we will need a total of 130 subjects.

### 10.6 MEASURES TO MINIMIZE IMIZE BIASC

NO
10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES

Each site will be provided a block randomization table with variable block sizes of 2, 4, and 6. The data coordinating center will continuously monitor the recruitment until the targeted sample size is reached. We will utilize the REDCap Randomization module for web-based randomization.

due then nature of the intervention and the clinical setting, this is a non-blinded trial.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, and health authority inspectors (or their agents) will have direct access to sourcedata and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for sourcedata verification, provided that patient confidentiality is maintained in accordance with local requirements.

Each Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient’s data. Examples of source documents are hospital records, office visit records; examining physician’s findings or notes, consultant’s written opinion or notes, laboratory reports, drug inventory, study drug label records, and CRFs that are used as the source.

Each Investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept for a minimum of 5 years. A publicly available dataset will be released per NIH guidelines.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Protocol Amendments: No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration. Each Investigator will sign the protocol amendment.

The IEC/EC may provide expedited review and approval/favorable opinion for minor change(s) in ongoing studies.

Protocol Deviations, Violations, and Exceptions: A protocol deviation is non-adherence to protocol-specific study procedures or schedule that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are reconsidered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e., non-adherence on the part of the patient, the Investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded by study center personnel.

No exceptions to protocol-specific entry criteria will be granted to allow patients to enter a study.

Information to Study Personnel: Each Investigator is responsible for giving information about the study to all study personnel involved in the study or in any element of patient management, both before restarting the practical performance of the study and during the course of the study (e.g., when new staff become involved). Each Investigator must assure that all study personnel are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study center authorization form, if required, which includes a clear description of each staff member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including each Investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study, and as otherwise agreed upon with the investigator or the study monitor.
The handling of data, including data quality assurance, will comply with regulatory guidelines (e.g., ICH and GCP) and the sponsor’s or its designee’s SOPs and working instructions. Data management and control processes specific to this study will be described in the data management plan. When data management is outsourced, the contractor organization will be responsible for the development and implementation of the data management plan.

**Data Quality Assurance:** All data on the CRF will be entered into a validated database compliant with 21 CFR Part 11 requirements. In the case when data management is outsourced, the contractor organization will be responsible for database quality assurance including, but not limited to, review of data entered into the CRFs by study center personnel for completeness and accuracy and instruction of the study personnel to make any required corrections.

Data management at Indiana University will implement edit checks on the eCRF to enforce data integrity and compliance to the protocol and regulatory requirements. Study center personnel will be responsible for reviewing the study data on the CRFs. Data management will track CRFs and review them for completeness, the presence of mandatory values, consistency, and dated electronic signatures. Queries identified during data discrepancy review will be sent to the study center personnel to be reviewed and resolved in a timely manner.

Adverse Events will be coded using the MedDRA dictionary. Concomitant medications will be coded using the WHO Drug dictionary. Adverse Events and Concomitant Medications will be reviewed for coding consistency and completeness.

At the end of the study, the database will be locked and the data will be released for reporting and statistical analysis.

### 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

#### 13.1 ETHICAL STANDARD

The Investigator(s) will conduct the study in accordance with this protocol, the guiding principles of the Declaration of Helsinki, ICH GCP guidelines and applicable regulatory requirements.

#### 13.2 INSTITUTIONAL REVIEW BOARD

Before this study starts, the protocol will be submitted to each IEC/IRB for review. As required, the study will not start at a given center before the IEC/IRB for the center provides written approval or a favorable opinion. The IRB will meet all FDA requirements governing IRBs (Code of Federal Regulations, Title 21, Part 56). The IEC will meet local regulations.

#### 13.3 INFORMED CONSENT PROCESS

##### 13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Each patient must be provided with a statement that the investigation involves research and that the IRB/EC has approved solicitation of patients to participate; a fair explanation of the procedures to be followed and their purposes, including identification of any procedures which may be experimental; a description in lay language of any possible side effects; a description of any attendant discomforts and risks reasonably to be expected; a description of any benefits reasonably to be expected; disclosure of any appropriate alternative procedures that might be advantageous for the patient; any offer to answer any inquiries concerning the procedures, and instruction that the person is free to withdraw consent and discontinue participation in the project at any time without prejudice to the patient. The informed consent shall include a disclosure that the Investigator is being supported by the NIH to perform the stated research.

##### 13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

A properly executed, written, non-consent is not required for the current U.S. federal code 21 CFR part 50, or competent regulatory authority; shall be obtained from each patient prior to entering the study or prior to performing any unusual or non-routine procedure involving risk to the patient.
A patient must give written consent to participate in the study. This consent must be dated and retained by the Principal Investigator as part of the study records. A copy shall be given to the patient. The informed consent process must be documented in the patient’s source documents.

Written or oral information about the study in a language understandable by the patient will be given to all patients.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Each Investigator must assure that the privacy and confidentiality of each study patient’s personal identity and personal medical information is maintained at all times. In order to maintain subject privacy and confidentiality, all CRFs, laboratory specimens, evaluation forms, reports, and other records, documents, and images that leave the site will be identified only by an identification code. This identification code shall on no occasion include study subject’s names, initials, or date of birth.

Information release or review of the personal health data of study patients shall take place solely within regulated and approved circumstances, and only to third parties, specifically identified by the written informed consent documentation signed by the study patients, except as permitted by applicable laws and regulations for purposes of monitoring and data verification by the relevant regulatory authorities, the NIH and NIH’s properly authorized representatives, or other regulatory authorities. Personal medical information will always be treated as confidential.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Each Investigator must keep a separate patient identification list showing code numbers, names, and dates of birth to allow unambiguous identification of each patient included in the study. A note will be made in the medical records that the patient is participating in a clinical study.

All required data will be recorded on the CRF by study center personnel according to the data entry guidelines provided by the PI or designee. All CRFs must be kept in good order and updated so they always reflect the latest observations on the patients participating in the study.

When paper CRFs are used, they will be completed legibly in black ink, with reasons given for missing data. Any corrections to the data will be made in a manner that does not obscure the original entry and will be dated and initialed by the Investigator or designee. Each Investigator will sign the statement on the last page of the CRF.

When electronic CRFs are used, electronic signatures of the Investigator (or designee) will be provided. Access to the electronic CRF will be controlled by the user identification and password, which are provided by the PI or designee. Study center personnel will be trained by the PI or designee in the use of electronic CRFs and the application of electronic signatures before the start of the study.

Because it is extremely important to have proper data collection in a timely manner, the Investigator shall complete the CRFs on an ongoing basis. If a study monitor is needed and study monitor requests additional data or clarification of data for the CRF, the request must be answered satisfactorily in a timely manner before the next monitoring visit.

14.2 STUDY RECORDS RETENTION

All records related to the study (i.e., source data, source documents, CRFs, copies of protocols and protocol amendments, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained for a minimum of 5 years.

Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the PI and NIH.
The Investigator will maintain all study records according to International Conference on Harmonization (ICH) - GCP and applicable regulatory requirements. Records will be retained for two (2) years following the date a marketing application is approved for the indication pertaining to this clinical study; or, if the medication is planned to be terminated or if regulatory application is not planned to be progressed, until two (2) years after the investigation is discontinued and the Food and Drug Administration (FDA), or competent regulatory authority, is notified.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is non-adherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e., non-adherence on the part of the patient, the Investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded by study center personnel.

No exceptions to protocol-specific entry criteria will be granted to allow patients to enter a study.

14.4 PUBLICATION AND DATA SHARING POLICY

RESOURCE SHARING PLAN

This includes the following activities:

- Publicizing the study as it is initiated, to trial investigators and other interested researchers
- Identifying and supporting proposals, (funding sources, implementation, analyses) for feasible salient ancillary studies;
- Providing a fully anonymized data set for future analyses/studies by interested researchers, once the trial funding has ended.

Each of these activities is discussed below.

Publicizing the Study

The key methods for publicizing the trial are:

- ClinicalTrials.gov – the government website that registers all initiated trials with trial protocol descriptions and contact information;
- The trial site PI’s and involved leadership group
- Design and rationale paper will be submitted for publication
- A final manuscript will be submitted after conclusion of the study.

Providing Access to Linked, Anonymized Data

On trial funding ends, two options will be:

- Provide the anonymized data set to NHLBI.
- Maintain the linked, anonymized data set via the IU Data Coordinating Center.

Regardless of which option is implemented, information on availability of data will be accessible on ClinicalTrials.gov and will be linked to other appropriate sites, including Indiana University websites.

PREPARATION OF THE ANONYMIZED, LIMITED ACCESS DATASET
To comply with NHLBI requirements for an adequately anonymized dataset, we propose the following activities for the dataset:

1. **Subject identifiers**:
   a. New random identification numbers without site identifiers will replace the original identification numbers. Once data acquisition is complete.
   b. The key linking the original and new ID numbers will not be provided to users of the anonymized dataset, nor to site investigators and staff.

2. **Variables that might lead to the identification of participants**:
   a. Interviewer or technician identification numbers or codes will be recoded or deleted.
   b. Regional variables with little or no variation within a center because they could be used to identify the center will be deleted.
   c. Unedited, verbatim responses that are stored as text data (e.g., specified in “other” category) will be deleted.

3. **Dates**: All dates will be encoded relative to a specific reference point (e.g., date of randomization). This provides privacy protection for individuals known to be in a study who are known to have had some significant event (e.g., myocardial infarction) on a particular date. Birth and other milestone dates will also be recoded relative to a specific reference date.

4. **Variables with low frequencies for some values**, that might be used to identify participants, may be recoded. These might include:
   a. Socioeconomic and demographic data (e.g., marital status, occupation, income, education, language, number of years married).
   b. Household and family composition (e.g., number in household, number of siblings or children, ages of children, number of brothers and sisters, relationships, spouse in study).
   c. Numbers of pregnancies, births, or multiple children within a birth.
   d. Anthropometry measures (e.g., height, weight, waist girth, hip girth, body mass index).
   e. Physical characteristics that are distinctive (e.g., blindness).
   f. Prior medical conditions with low frequency (e.g., group specific cancers into broader categories) and related questions such as age at diagnosis and current status.

5. **Race/ethnicity and gender information** when very few subjects are in certain groups or cells.
   a. Polychotomous variables: values or groups will be collapsed so as to ensure a minimum number of subjects (e.g., at least 20) for each value within each race - gender cell.
   b. Continuous variables: distributions will be truncated if needed to ensure that at least 20 subjects (e.g., at least 20) have the same highest and lowest values in each race - gender cell.
   c. Dichotomous variables: data should be grouped with other related variables so as to ensure a minimum number of subjects (e.g., at least 20) in each race - gender cell or deleted.

**CLINICAL TRIALS.GOV**

This study will be registered at the appropriate and required time by the PI, in conjunction with the DCC, to the government-operated clinical trial registry database, which contains registration, results, and other information about registered clinical trials at ClinicalTrials.gov. Federal law under FDAAA requires clinical trial information for certain
clinical trials to be submitted to the data bank and this study will comply with all reporting requirements for clinical trials.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

This study will be conducted at 3 sites in the United States, with 4 total hospitals. Site 1) Indianapolis, IN at both the Eskenazi and Methodist hospitals (abbreviated as IU, Peter S. Pang, PI), Site 2) Nashville, TN at the University of Vanderbilt hospital (abbreviated as Vanderbilt, Sean P. Collins, PI), Site 3) Detroit, MI at the Detroit Receiving Hospital Center (abbreviated as DRC, Philip D. Levy). Each site PI will be a member of the steering committee. Dr. O’Connor at INOVA will serve as Chair of the Steering Committee.

The following diagram illustrates the relationship between the DSMB and other entities in this study.

Communication with DSMB members will be primarily through the NHLBI Program Office and the Data Coordinating Center (DCC) housed at IU. The primary coordinator of data transfer between them will be each team and the DSMB will be the DCC working with the DSMB statistician, who will also be at IU (TBD). It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls. The Steering Committee will be comprised of the Site PI and LUS PI at each site.
**CONFLICT OF INTEREST POLICY**

All investigators must adhere to national, regional, and local conflict of interest policies. Prior to publication, all disclosures potentially relevant to this trial will be explicitly stated.

**ADDITIONAL TRAINING MATERIALS**

17.1 LUNG ULTRASOUND TRAINING OVERVIEW

**Lung Ultrasound Training Overview**

Each clinical site already has expertise in LUS (lung ultrasound). However, to minimize variation, a standardized teaching format will be utilized, emphasizing the 8 zone scoring system. Videos perform better to explain LUS and B-lines than a word document or PDF. Videos will be utilized for training purposes, however, a document representation is listed below.

**Why use lung ultrasound?** For all of the following reasons:

- It is fast
- No radiation
- Non invasive
- Repeatable

Ultrasound has been used at the bedside for years. Machines continue to get smaller and smaller and easier to move around.

What is the difference between focused ultrasound and formal echocardiography or radiology studies? Focused ultrasound does not replace formal echocardiography or formal radiology studies. It is meant to answer a binary clinical question. For the purpose of our study, it is meant to guide AHF management. [The figure below with red arrows shows examples of B-lines]
Lung (or pulmonary ultrasound) is one of the easiest ultrasound assessments to learn and perform. Even in patients with a high BMI, the lung can be evaluated. Additionally, lung ultrasound has high inter-rater agreement.

In this figure to the left, we are seeing B lines – vertical echogenic artifacts originating from the pleural line, extending to the bottom of the ultrasound screen and moving with lung sliding. In AHF patients, B-line assessment aids in diagnosis, prognosis and may guide acute management.

Below is the curvilinear probe used for the images.
Below is a pictorial representation of the 8-zone scoring system.

The eight zone protocol breaks each hemi-thorax into 4 zones, divided by the parasternal (PS) Line, Ant axillary line (AAL), posterior axillary line (PAL) and anatomic nipple line (ANL). In the clinical setting of suspected AHF, pulmonary edema is determined sonographically as greater than three B-lines in a rib space in at least two lung zones bilaterally. For scoring purposes, a B line cut off of 10 has been described previously in the literature. This allows for a more precise quantification of pulmonary edema. B lines will be counted as the number seen per acoustic window.

Machine settings

- Enter patient data
- Select **curvilinear** probe
- Select thorax exam
- Set **depth** to 18 cm
- Set **clip length** to 6 seconds
- Turn off tissue harmonics and multi-beam former
- Adjust **gain** so that the rib shadow is black and pleural line is distinct
Image acquisition

- Patient supine
- 45 degrees of bed elevation (as possible, if not possible please note on CRF)

Starting off on the **Right** in **Zone 1**: you want the indicator towards the patient’s head. Identify ribs by shadowing and identify a rib space (see image below)
- Label R1
- Then turn 90 degrees with **indicator towards patient’s right** so you are still in a rib space but the probe is **HORIZONTAL**
- Scan within the zone until you see the area of most B lines
- Record 6 second clip (this should include both inspiration and expiration)
- Repeat the above for Right zones 2-4 and Left zones 1-4
- Obtain **VERTICAL** R4 and L4 zones
- 10 TOTAL videos
- After you leave the bedside, record the number of B lines on a standardized data collection form or in REDCap
COUNTING B LINES

- B lines are vertical echogenic artifacts that originate from the pleural line and extend to the bottom of the ultrasound screen
- Below image is an example of how to count individual B lines

Figure 3: Counting of B-Lines using Lung Ultrasound
• In the situation where the whole footprint is ‘white out’ (see below image) count as 20 B lines
• The maximum number of B lines per sector is 20
• Count the maximum number of B lines you see
• If half of the footprint is a ‘white out’ count as 10 B lines
• Estimate percentage of white out
• Count up and down from there

For lung ultrasound we rely on the imaging of artifacts to interpret our scans. The main artifact in the lung we see is called reverberation artifact. The physics behind this artifact is briefly explained below.

The ultrasound probe is constantly sending ultrasound waves towards whatever tissue is being imaged. When these sound waves get caught between 2 parallel surfaces that are highly reflective, they can bounce around between these highly reflective surfaces and take longer to return to the ultrasound machine.

When this happens, you can have an echo that returns to the transducer after a single reflection and this echo will be displayed on the machine in the proper location. Sequential echoes may take longer to return to the
transducer, and due to this increase in time the machine thinks that it is from a surface further away so it will appear deeper on the ultrasound image. So what you end up seeing are bright arcs that occur at equidistant intervals.

Below are examples of normal lung, Bat sign, and A lines.

Pleural line and recurrent A lines or reverberation artifact. We see this in normal lung and patients with COPD.
The figure below shows B lines. These are vertical echogenic artifacts that originate from the pleural line, extend to the bottom of the ultrasound screen.

Normal patients have < 3 B lines per rib space
B lines may be seen outside of AHF. Clinical context is crucial! The table below shows other reasons why B lines may be present.

<table>
<thead>
<tr>
<th>FOCAL</th>
<th>DIFFUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct</td>
<td>Pulmonary Edema</td>
</tr>
<tr>
<td>Contusion</td>
<td>ARDS</td>
</tr>
<tr>
<td>Cancer</td>
<td>Pulmonary Fibrosis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia/Pneumonitis</td>
</tr>
</tbody>
</table>
Beware if you do NOT see A lines! Below are coalesced B lines. So many B-lines blend together, it could look like normal lung but you note no A lines. (This appears better in video). This is, in fact, diffuse B lines.

17.2 ULTRASOUND SECURE TRANSFER PROTOCOL

We have previously utilized BOX, an online cloud storage and collaborative environment. Under the strict supervision of Indiana University data stewards, we continue to utilize BOX HEALTH. Such accounts can only be set up via application to the IU data stewards for storage of critical health data. Access to these secure storage sites is shared with vetted users. Two dedicated BOX HEALTH accounts will be set up for BLUSHED AHF.

All sites currently use Q Path, a vendor-based ultrasound storage system. All sites plus the Core Lab use Q Path in their day-to-day storage and review of US images. Images are securely transferred via wireless transmission from US machines to Q Path with PHI. All images are stored securely under HIPAA-graded security systems. From Q Path, images are then exported to individual computers. During this transfer, PHI is NOT transferred. The only identifying cues left are date/timestamp, which may also be removed. Additional, non-identifiable labels will be added for study purposes. These will then be uploaded into BOX HEALTH.
Two BOXHEALTH folders will be created, one for the investigators and the other for the Core Lab. Prior to uploading to the Core Lab, the images will be de-identified to site by the database manager. Furthermore, the images will be scrambled to avoid interpretation by acquisition order. This further minimizes bias by forbidding site knowledge and order of acquisition. The de-identified images (both by site and PHI) will then be uploaded to the Core Lab BOX HEALTH storage folder for review by the Core Lab.

All interpretations by the Core Lab will be entered into REDCap.

17.3 CORE LAB PROCEDURE AND LUNG ULTRASOUND PROTOCOL

Introduction

The B-lines Lung Ultrasound Guided ED Management of Acute Heart Failure (BLUSHED-AHF) is designed to assess the short-term effectiveness of early LUS guided, protocolized, ED AHF management compared to usual care. ED patients with AHF, who meet all other eligibility criteria, will be randomized within 3 hours of presentation. To achieve this goal, a randomized, controlled, multi-site, strategy-of-care, pilot trial is proposed.

The correlation between B-lines on lung ultrasound and AHF has been well-established. B-lines are an assessment of extravascular lung water (EVLW). Past studies demonstrate correlation of B-lines with the following: (1) natriuretic peptide levels, (2) invasive hemodynamics, (3) chest x-ray, (4) clinical assessments, and (5) computed tomography. Moreover, B-lines may resolve after treatment. Lung ultrasound has an additional advantage: it measures patient’s clinical status in real-time. Finally, lung ultrasound is easily reproducible and does not carry any radiation exposure risk; thus, it can be repeated at regular intervals without increased risk to the patient.

Lung Ultrasound (LUS) Protocol

To best determine the potential value of EVLW measurements using LUS, we will assess patients at multiple timepoints throughout hospitalization. (See Figure 1 – Trial design flow below)
For diagnostic purposes, previously published protocols have been the most well-studied. Each LUS scan consists of 8 sectors as seen in figure 2. (Figure reproduced from Volpicelli et al. 7) Trained research personnel will record and count B-lines in each sector as visualized through a respiratory cycle at each of the time points listed in the figure. At minimum, each stored video clip will be 6 seconds in length. The total number of B-lines for all 8 sectors will comprise the overall score. With training, the entire scan takes less than 10 minutes.

As patient positioning may impact B-lines, patients will be placed at approximately 45 degrees for all scanning. The CRF will be marked if patients are unable to lie at this angle.

- An 8 zone LUS scan will be done at the following times:
  - T00: initial LUS scan (in ED for screening and eligibility)
  - T02: 2-4 hours after initial treatment (in ED) (+/- 30 minutes)
  - T06: 2-4 hours after T02 or pre-ED discharge, whichever comes first (+/- 60 minutes)
  - HD2: 24 hours after initial scan (Day 2) (+/- 6 hours)
  - HD3: 48 hours after initial scan (Day 3) (+/- 8 hours)
  - HD4: Day 4 (any time during day)
  - HD5: Day 5 (any time during day)
  - HD6: Day 6 (any time during day)
  - HD7: Day 7 (any time during day)

- If standard care arm do NOT notify the provider of the results

Data Collection Form

- B lines
- Pleural effusion size and location
- Who is performing the scan
- Document time to perform scan
  - Begin with time stamp of first image and end with time stamp of last image +6s

Training

- Fill out pre-survey
- Watch training video on LUS and scanning protocol (15-20 minutes)
- Review 23 clips together with US director (20 minutes)
- Hands-on scanning (30 minutes)
- Perform 25 clips that have been reviewed by US director and signed off on prior to enrolling a patient (>75% of clips have B lines)
- 20% clips are reviewed by LUS Core Lab (Vicki)
- Correlation coefficient

**Materials**

Each site will have an ultrasound machine capable of performing video image recording as well as a low frequency curvilinear or abdominal (2 - 5 MHz) probe. B-lines are US artifacts and machine software may attempt to 'clean up' images, thereby minimizing the appearance of B-lines. Therefore, machine settings at each site will be optimized for B-line visualization. To ensure consistency, the same machine with the same settings will be used for serial exams.

To the extent possible, it is preferable that sites use the same machine to facilitate standardization. For example, if the emergency department has a Sonosite Micromaxx or later model, we can standardize the protocol so that the depth is set at 18 cm, the probe is the 2 - 5 MHz abdominal probe, and the settings are the abdominal preset. For sites that do not have the same equipment, a standard scanning protocol will be established for each specific machine, with the following requirements:

1) A low frequency curvilinear probe will be used for all image acquisition (2 - 5 MHz)
2) The depth will be set to 18 cm
3) The gain settings will be standardized for all scans at each specific site. If equipment is the same, the gain will be standardized.

**Training**

All physicians and research staff will undergo in-person training sessions led by the US PI at each site using a standard protocol. Both didactics and proctored bedside scans will occur. This will ensure technique and equipment settings are standardized. Published literature provides strong evidence that LUS can be learned with minimal training: as little as 30 minutes yield excellent ent correlation with expert sonographers. In addition, established protocols will be utilized for transfer and storage of images.
To ensure ongoing quality assurance, feedback will be provided to each site for every 10 patients, or more frequently as needed. Initial reviews suggest inconsistency. An independent, blinded, expert ultrasonographer will review the images. Concordance with clinical site interpretations will be provided. Additional training will be provided by the central reviewer as needed. Inter-rater agreement on B-line counts will be reported at the end of the study.

The CORE lab is led by Vicki Noble MD; she is an internationally recognized expert in LUS. She has a proven record of training, both for research and clinical purposes. She has substantial experience in the collation, interpretation, and reporting of LUS images.

**Counting of B-lines:** (Figures courtesy of Luna Gargani MD)

Blines will be counted as the number seen per acoustic window. See Figure 3.

In the situation where there is ‘white out’ or diffuse B lines in a rib space, this will count as 10 B lines. Half the rib space will count as 5. 10 will be the maximum number of B lines per sector.

**Image Review**

All images will be saved as 6-second video clips. Investigators or study staff will label each clip with the time of scan post-enrollment. For example, Scan 0 is at time of enrollment. Scan 24 is 24 hours post-enrollment. All images will be sobedate/time-stamped, which will be recorded in the local site CRF. Investigators or study staff will fill out a table of their count of B lines, which will be compared to the Core Lab review. If a rib space is completely white out with B lines, this will count as 10 B lines, half the rib space will count as 5. Importantly, the Core Lab will be blinded to the investigator B-line count.

No PHI will be recorded, only a study ID. Each site will separately and securely store linkages from PHI to the study ID per local IRB-approved protocols. Currently, all sites have internal processes to store images for quality control as part of their training programs for fellows and residents. Images will then be transferred to a secure, password-protected, access-limited server with HIPAA-grade security.

Local sites will review images to ensure deidentification. Once deidentified, images will be uploaded to a secure, local server with HIPAA-grade security. No post-processing will occur. However, prior to upload to the Core Lab, images will be deliberately mixed with other study patients. This is being done to avoid readers from having ‘before and after’ images. Images will be then uploaded in batches of 5 patients to a secure, HIPAA-grade server. The Core Lab will then download the images. Importantly, the Core Lab will NOT be a study site to minimize any potential bias or failure of deidentification. Furthermore, the Core Lab will not have access to any clinical information on the patient, further limiting the potential for clinical information bias. Image interpretation is performed by the Core Lab, which may not see images from other sites. Reviewers will not see images of patients in chronological order or from only one site at a time.
Formal interpretations will be recorded on a standardized, secure CRF accessible only to the Core Lab and the Data Coordinating Center at IU. All investigators will NOT have access to this data until database lock. Applicable backup and secondary storage will occur on a daily basis.


35. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33(14):1787-1847.


