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 needs to occur during the ER stay. The final pre-discharge draw needs to occurs as soon as possible prior to discharge.
- The reassessments have been modified. Rather than every 2 hours in the ED, a minimum of two re-assessments will occur. The first within 2-4 hours of first treatment. The second 2-4 hours after the first OR pre-discharge from the ED, whichever comes 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 200mg 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 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 treatmet to continue.
- Editing and clarifications were also added

Verion 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 b/c 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.

Table of Contents

LIST OF ABBREVIATIONS

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

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 [21CFR] 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 would be 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 described 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: Phillip Levy, MD

Institution Address:

Detroit Receiving Hospital	Sinai Grace Hospital
4201 St. Antoine	6071 W. Outer Drive
Detroit, MI 48201	Detroit, MI 48235

Signature: _____   Date: 20 - AUG - 2018

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 dead or re-hospitalized 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

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 start up, 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

SCHEMATIC OF STUDY DESIGN

Figure 1: Trial Schematic
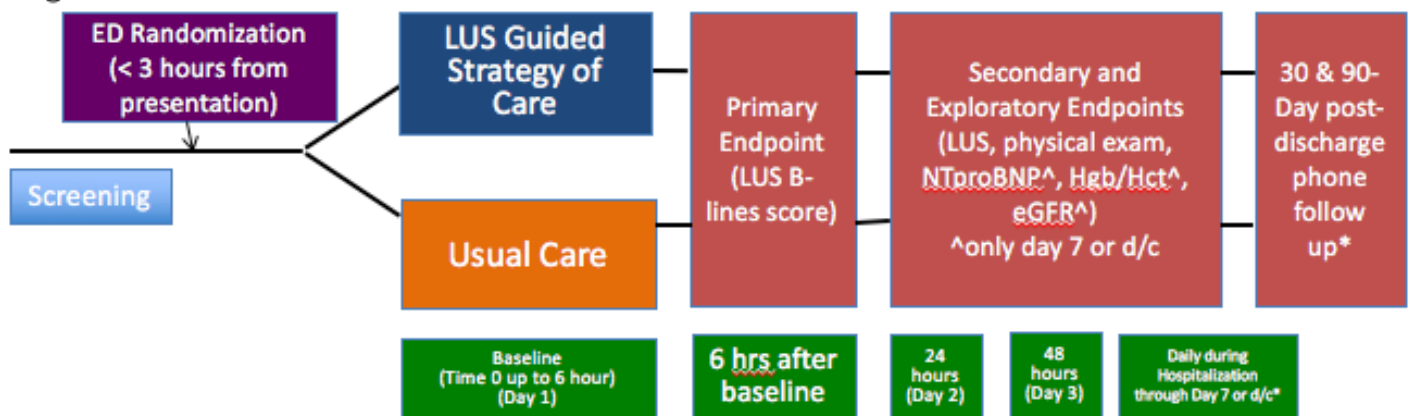
*whichever comes first

^only if part of standard of care. Only NTpro and hsTnT 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 reviwer

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 the site 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 dead or re-hospitalized.[25] By one year after hospitalization, up to 67% of patients will be re-hospitalized and 36% will be dead.[26] Worldwide, the costs of AHF exceed 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 reductions in morbidity and mortality for chronic HF, considerably 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, associated with greater morbidity and mortality.[32,33] One of the most expensive decisions in healthcare is made routinely from the ED; who gets hospitalized vs. discharged. Despite this crucial starting role, **ED AHF pharmacological management today is largely same as 40 years ago.**[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 a working group from the NHLBI on ED AHF management further corroborate this lack of evidence: *"the evidence base on which this foundation of acute care is built is astonishly thin*."[9,12] There remains a critical unmet need for evidence based ED AHF 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. Yet how to best assess, grade, and manage congestion is not well established.[39,41] Only recently has the dosing of IV loop diuretics been studied; however patients were enrolled up to 24 hours after admission.[33]

2.2   RATIONALE

Limitations of Current AHF Therapy

There are currently no Class I, Level of Evidence A therapeutic guideline recommendations for AHF, highlighting the unmet need.[4,5] In fact, therapeutic recommendations from the ACCF/AHA begin with hospital based management, highlighting the absence of ED based evidence.[37] The last ED based guidelines were published in 2007 and have yet to be updated.[42] We argue this 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;[43-48] yet many patients leave the hospital inadequately decongested.[43,49-52] In fact, many patients leave the hospital without a pre-discharge assessment of congestion.[38,39] We would argue 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.[39,53] A recent consensus statement published in 2010 highlights this fact: **"…no method to assess congestion prior to discharge has been validated."**[39] While physical exam is currently the cornerstone of congestion assessment, it lacks sensitivity and inter-rater reliability.[53,54] The ED is the beginning of AHF management for >75% of admitted patients;[55,56] delays in diagnosis, misdiagnosis, and resultant delays in management are associated with greater morbidity and mortality.[32,33]

Figure 1: LUS B Lines

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.[57,58] However, in the setting of pulmonary congestion, extra vascular lung water (EVLW) can be directly visualized and quantitated.[58-60] Lung ultrasound measurement of B-lines are an objective, semi-quantitative measure of extra vascular lung water (EVLW).[60] B-lines are well-defined, vertical echogenic lines, originating from water-thickened interlobular septa.[60] (Figure 1) They are a marker of congestion.

LUS improves diagnostic accuracy and is highly reproducible.[61-67] Intra and inter-observer variability of B-line capture and summary have been reported as low as 5.1% and 7.4%, respectively.[68] 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)).[61] This may reflect the additional value of LUS when patients have chronically elevated NP levels. Recent guideline and consensus statements also support the use of LUS for diagnosis.[69-73]
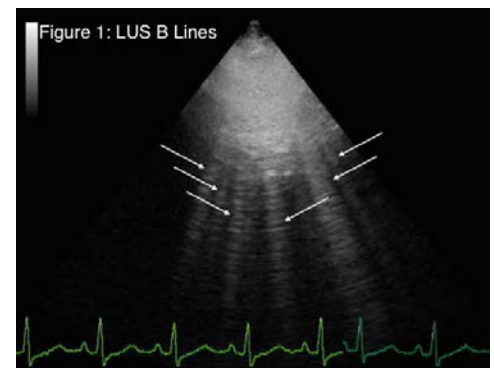
Importantly, B-lines are a dynamic marker. In dialysis patients, B-lines decrease markedly pre/post dialysis.[74] In AHF patients, B lines generally decrease throughout hospitalization.[75,76] However, persistence of B-lines pre-discharge identifies patients at higher risk for worse outcomes.[76,77] B-lines even outperformed BNP as a prognostic marker.[75] Finally, serial measurement of B-lines are both easy to learn and perform.[62,63,78-80] LUS is also low cost, and does not involve radiation. Computerized diagnostic aids have already been pilot tested with excellent results, demonstrating the ease of B-line scoring.[81] Hand held machines perform as well as a standard ECHO platform or US machines.[63,82] **The ease of LUS will facilitate its generalizability and dissemination.** Non-physicians may be future users of bedside LUS assessment, further supporting its generalizability.

We will also perform serial measures of LUS during hospitalization to further study its prognostic significance.[75,76,83] By capturing treatment during hospitalization, we will better understand the trajectory of LUS B-line resolution, and determine whether future studies should continue to target LUS B-lines during inpatient therapy. We will also track physical exam, NTproBNP levels, eGFR, and hemoglobin/hematocrit levels as other measures of decongestion, to better understand the downstream impact of ED care.[50,84,85] This will allow us to better discriminate the value of LUS compared to other measures.

Figure 2

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 lines 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 pre-specified cut-off of 15 B-lines as a marker of persistent pulmonary congestion, 50% of patients had evidence of EVLW at Td. The 28 sector scoring method was utilized.[60,64] The average number of B-lines 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.
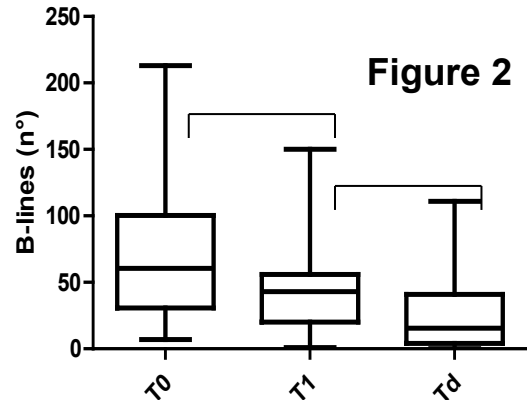
Figure 3: Prognostic Value of LUS
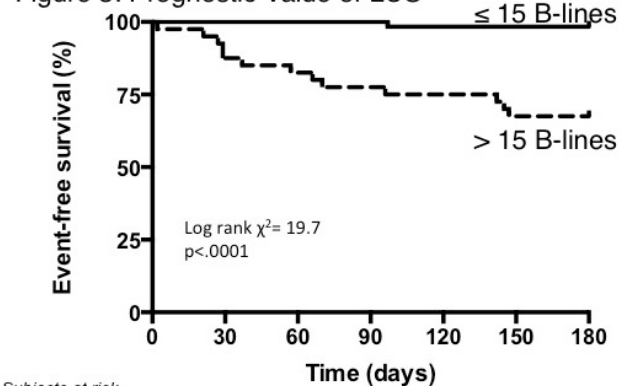
During the follow-up period (median: 58 days, interquartile range: 44-82 days) 15 events occurred: 2 deaths and 12 all-cause re-hospitalizations. In the subset of patients who experienced events during follow-up, 93% were discharged with persistent presence of pulmonary congestion (> 15 B-lines) as measured 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 lines at discharge (20+/- 23) vs. admission (48+/-48, $p<.0001$). At 6-month follow up, patients with ≥ 15 B-lines at discharge were significantly more likely to be re-hospitalized. (HR 11.7 (95% CI 1.3-106.6) (See Figure 3).[76] In 27% of patients with >30 B-lines, no rales were reported by auscultation.

Additional work performed by one our study team members, Vicki Noble, demonstrated a strong correlation between LUS B-lines and patients undergoing dialysis. This proof of concept supports B-lines as responsive to the removal of fluid.[74] Coiro et.al. recently published a study of LUS performed throughout hospitalization, demonstrating the prognostic significance of residual congestion, as measured by B-lines.

Patients with ≥ 30 B lines had significantly worse combined outcome of all-cause mortality and HF re-hospitalizations at 90 days.[75]

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 evidence supporting the use of IV loop diuretics. The evidence is even 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 risk may or 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 over diuresis 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 failure to decongest is associated with greater risk for adverse outcomes than transient AKI. To add a margin of safety, only patients with an eGFR ≥45 will be enrolled. Finally, we will assess eGFR prior to discharge (if measured as part of standard of care) to better understand whether our proposed strategy-of-care is associated with worsening renal function. For nitrates, 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 a SBP > 110mmHg 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 as endotracheal intubation. No patients who are unable to protect their airway will be placed on NIV. Patients may also complain of claustrophobia or discomfort with the tight fitting mask. Attempts to adjust accordingly will be made. Anecdotally, patients feel significantly better and usually the improvement outweighs the discomfort. Other issues such as skin necrosis from long-term use of NIV does not apply to the short-term use of NIV.

An unknown risk is whether or not 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 as potential electrolytes, eGFR, and pre-specified NTproBNP and Hgb/Hct will require additional blood draws, however, 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 ordered.

2.3.2 KNOWN POTENTIAL BENEFITS

Patients enrolled in this study who are receiving the strategy-of-care or usual care may receive a benefit such as decreased mortality, or less frequent hospitalizations related to HF, or feel better faster, or have less myocardial injury,

AHF patients, if this study demonstrates sufficient safety to then test in a future efficacy study, which if positive will show that and 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 our specific aims will provide the necessary and sufficient information to determine whether a LUS guided ED strategy leads to more rapid and sustained decongestion. A 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.[6,86] If successful, we may expand the patient population in future studies. However, the following critical issue needs 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 above and beyond usual care? 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 exclude patients in cardiogenic shock or hypertensive emergency.[6,86] 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 pilot 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 these results to minimize contamination 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 1:1 to our LUS-guided strategy-of-care vs. usual care. While no 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-specified 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 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 life threatening 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 a priori 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 3: Exploratory Endpoints	
Total DAOOH through 30 and 90 days post-discharge	Association of B-lines at discharge and 30 and 90 day outcomes
Change in biomarkers from presentation to pre-discharge	Association of baseline, discharge, and change with 30 and 90 day outcomes
Time to reach B-lines <15	B lines < 15 at 24 hours and at discharge
Composite of 30-day all-cause mortality, cardiovascular (CV) re-hospitalizations, 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] Also for same endpoint, but through 90 days	All Cause readmissions, All cause ED re-visits
Change in physical exam findings and body weight from presentation to pre-discharge	Description of ED pharmacologic treatment
Description of hospital based AHF treatment	Inter and intraobserver agreement

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) Hx 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$_{ml//min/1.73m^2}$.

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

3) SBP < 100 or > 175mmHg

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 >101.5ºF

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

8) Anemia requiring transfusion

9) Known interstitial lung disease

10) Suspected acute lung injury or acute 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 that 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 this 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, to make it possible for the patient to continue to participate 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 in 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 AGENT(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.

```
                                    ┌─────────────────────────────────────┐
                                    │  IV furosemide (unless already given)│
                                    │  -2x single oral dose if on chronic  │
                                    │           therapy                    │
                                    │     -20-40mg if diuretic naive       │
                                    └─────────────────────────────────────┘
                                                      │
                                                      ▼
┌──────────────────────────────────┐   ┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐
│        Restart Algorithm*         │   │       Optional Therapies      │
│  IV Diuretic Options              │──▶│   1. NIV – non-invasive       │
│    1. 1x single oral dose if      │   │         ventilation           │
│       on chronic therapy          │   │   2. Vasodilators (SL,        │
│    2. Repeat original IV dose     │   │         topical, or IV)       │
│    3. Double original IV dose     │   └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
└──────────────────────────────────┘                 │
                    ▲                                 ▼
                    │                   ┌─────────────────────────────┐
                    │                   │        Reassess**           │
                    │                   │  Arm 1: LUS + Clinical      │
                    │                   │         Assessment          │
                    │                   │  Arm 2: Clinical Assessment │
                    │                   │         alone               │
                    │                   └─────────────────────────────┘
                    │                                 │
                    │                                 ▼
                    │                          ╱──────────────╲
                    │                         ╱  Goal Achieved? ╲
                    │            NO          ╱  (clearing of     ╲
                    └───────────────────────   B-lines vs.        
                                             ╲  clinical          ╱
                                              ╲ improvement      ╱
                                               ╲    alone       ╱
                                                ╲──────────────╱
                                                      │ YES
                                                      ▼
                                    ┌─────────────────────────────────────┐
                                    │            Disposition               │
                                    │       Admission or Discharge         │
                                    └─────────────────────────────────────┘
```

- All enrolled patients should receive IV furosemide per the protocol box.
  - 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 to equal 2x single oral dose. For example, if the patient usually takes 80 BID at home, but then already received 40mg at arrival to the ED, if in the LUS arm, would receive an extra 120mg. (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, these results will NOT be shared with clinical caregiving team

** ALL enrolled patients will be re-assessed at least twice during their ED stay. First re-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 re-assessment will occur EITHER 2-4 hours after the first OR prior to discharge. IF the pre-discharge assessment is missed in the ER, this should occurs ASAP after arrival to the hospital floor.

NOTE: the maximum dose allowed at any one timeof IV Lasix is 200mgIV.

NOTE: For additional 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) uptitration 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. If, in the opinon of the investigator, the protocol should not be continued once 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 opinon of the investigator, the protocol should not be continued once 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 study specific procedures.

7.1.2 STANDARD OF CARE STUDY 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 lab work is not drawn, the closest clinical lab draw will be recorded in the eCRF unless already recorded (i.e. the baseline value). NO labs, other than for 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 underlying disease state by the Investigator using the following categories:

- abnormal but not a clinically-significant worsening

- abnormal and a 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, or 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 0.5mL discard sample will be taken if the catheter was flushed with saline.

2 aliquots per sample type per collection = 6 total aliquots

Time Point	Tube Type	Blood Volume
T0 = 0 hour (Baseline)	Serum Separator	One tube, ~ 4cc
	Lithium Heparin	One tube, ~ 4cc
	EDTA Plasma	One tube, ~ 4cc
	Serum Separator	One tube, ~ 4cc

T1 = Day 7 or discharge +/- 24 hours	Lithium Heparin	One tube, ~ 4cc
	EDTA Plasma	One tube, ~ 4cc

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 allowing 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 0.5cc of supernatant for each aliquot, with 2 aliquots per tube. DO NOT MIX or POOL supernatant from separate pools together.

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

Freezers must have temperature logs available for review.

7.2.4   SPECIMEN SHIPMENT

Frozen biomarker 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 -20C or lower 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 their 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 (includes 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 time stamp when patient placed in a room to be seen by a provider. Waiting room time does not count. Randomization will occur via 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

Schedule of Events	Screening	Day 1 T00	Day 1 T02-04	Day 1 T06	Day 2-6 T24-D6	Day 7 or D/C*	30 & 90 day follow up	Quarterly
Informed consent (I/E)	X							
Medical History	X							
Medication history	X							
Clinical Assessment#		X	X	X	X	X		
Body Weight, height, Vital Signs	ED SOC	VS only	VS only	VS only	BW/VS only	BW/VS only		
Labs: Electrolytes, hematology, NP, eGFR, Troponin	ED SOC							
NT-proBNP / hsTroponin (for central lab processing)		X				X		
12-lead ECG	ED SOC							
CXR	ED SOC							
LUS B-lines 8 zone	X (LUS T00)		X	X	X	X		
LUS Guided AHF Management or Usual Care		X	X	X				
Lab draw: eGFR, Hgb/Hct^		X				X*		
Prep and Storage of Samples		X				X		
eCRF/data collection/verification		X					X	

							X	
Assessment of AE/SAE's							X	
Phone follow-up Vital Status							X	
Batch shipment of samples								X
Subject payment		X					X	

SOC = standard of care, ED = Emergency Department, I/E = inclusion, exclusion, CV = cardiovascular, LUS = lung ultrasound, BW = body weight, 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 per form for ED phase

Further detail 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]

- o T00: initial LUS scan (in ED for screening and eligibility)
- o T02: 2-4 hours after initial treatment (in ED) (+/- 30 minutes)
- o T06: 2-4 hours after T02 or pre-ED discharge, whichever comes first (+/- 60 minutes)
- o HD2: 24 hours after initial scan (Day 2) (+/- 6 hours)
- o HD3: 48 hours after initial scan (Day 3) (+/- 8 hours)
- o HD4: Day 4 (anytime during day)
- o HD5: Day 5 (anytime during day)
- o HD6: Day 6 (anytime during day)
- o 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 signs 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 investigators discretion should there be any concern for the patients 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, re-hospitalization, and ED visits through 90 days will be assessed for safety as well as efficacy

Hypotension, defined as a SBP < 100mmHg, will be assessed as a safety endpoint. SBP Decrease Safety Margin: Patients whose SBP decreases to < 100mmHg 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 > 100mmHg 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 the following:

• 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 day 5 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).

• It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The severity of each adverse event must be recorded as 1 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 in accordance with 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, inter-current 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, inter-current 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, acute renal 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, elevated BNP 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 analgesia, need for skilled nursing facility upon

discharge, need for early follow up with physician, escalation of heart failure therapy, need for cardiac catheterization or PA 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.

The onset 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 SAE's will be reviewed within 48 hours and all AE's 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 IRBs 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

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, NTproBNP, and hemoglobin/hematocrit levels will be assessed to determine the superiority or additive value 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 patient 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 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 in the treatment group to which they were randomized. Results of analyses in this analysis population 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 Fishers exact test, as appropriate.

The use of prior and concomitant medications will be summarized. The use and doses of IV and oral loop diuretics in furosemide equivalents will be summarized by treatment group. Other concomitant medications will be coded using WHO Drug 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 hemoconcentration 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.[88-90] For hemoconcentration, any increase in value in both hematocrit and hemoglobin during hospitalization will be considered positive.[84] 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 treat DAOOH as an ordinal outcome and use the proportional odds (PO) regression model to compare the two arms. The PO model is a generalization of the Wilcoxon (Mann-Whitney) test to estimate the shift in the underlying 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 area under the curve (AUC) calculated to understand the prediction performance of the B-line measurements. Sensitivity, specificity, positive and negative predictive values will be computed at a number of thresholds of B-line measurements to understand the trade-off between false positive and false negative. Confidence intervals of statistical measures will be constructed using the bootstrap method.[91] Although 15 B-lines have been previously identified as a valid threshold, an alternative number may be more useful in the ED setting.

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.

We will compare parameters used to identify congestion. This will include a comparison between B-lines measurements and other markers, such as physical exam, NTproBNP, eGFR, and hemoglobin/hematocrit. Bootstrap method will be used for the comparison to account for correlations between the markers and the B-line measurements. 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 together with B-line measurements in the model (Model 1). Second, we will explore all main effects models that can be built using the B-line measurements along with the other markers and select the one with the best model fitting characteristic (e.g. Akaike 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[92] 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.[93,94] 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 Fishers exact test, as appropriate.

As all cause mortality and re-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),[95] 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 a multiple imputation[96] 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 an un-observed outcome, potential bias can be introduced if the miss-data mechanism is ignored. 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 [97], pattern mixture model [95], or latent variable model [98] 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% 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 ED AHF management. With 59 patients in each of the two arms, 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 BIAS

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 the nature of the intervention and the clinical setting, this is an unblinded trial.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for source data 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 finding 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 publically 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 IRB/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 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.

Information to Study Personnel: Each Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting 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 staff members 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 either 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 a data management plan. When data management is outsourced, the contract 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 contract 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 entering study data on the eCRFs. Data management will track eCRFs 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 are 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; a disclosure of any appropriate alternative procedures that might be advantageous for the patient; an offer to answer any inquiries concerning the procedures, and instruction that the person is free to withdraw consent and discontinue participation in the project or activity 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 consent in compliance with current U.S. federal code 21CFR 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 and/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 image material 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.

Medical 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 document 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 assigned designee. Each Investigator will sign the statement on the last page of the CRF.

When eCRFs are used, electronic signatures of the Investigator (or designee) will be provided.

Access to the eCRF for data entry and signature is controlled by 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 eCRFs and 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 and 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 a 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

Once 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 data set:

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 data set, 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 coded 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 or step-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 a minimum number of subjects (e.g., at least 20) have the same highest and lowest values in each race-gender cell.

   c. Dichotomous variables: data should either 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 data bank, 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.
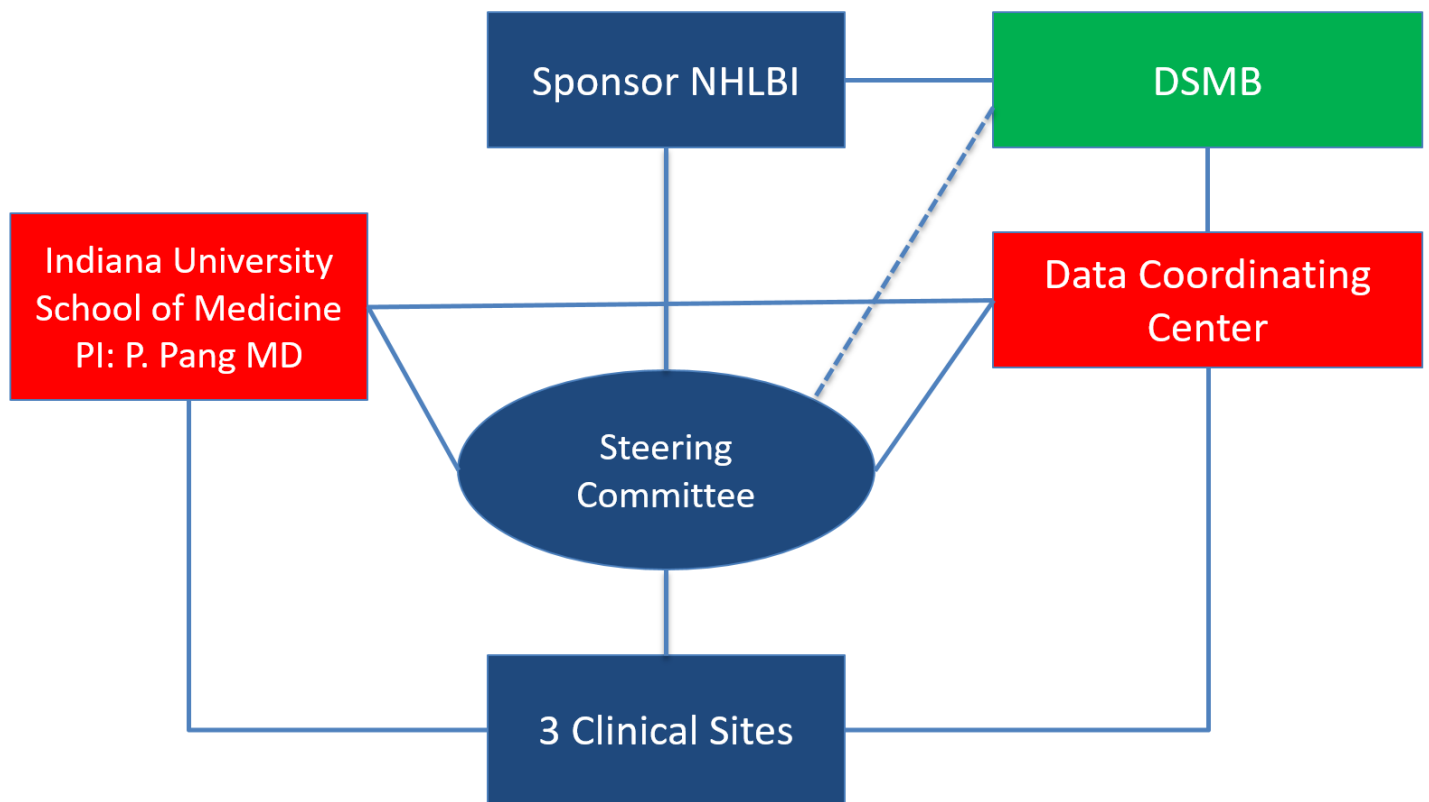
Communication with DSMB members will be primarily through the NHLBI Program Office and the Data Coordinating Center (DCC) housed at IU. The primary coordinator of data transfer between the research team and the DSMB will be the DCC working with the DSMB statistician, who will also be at IU (TBD).   It 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.

16   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.

17   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:

a. It is fast
b. No radiation
c. Non invasive
d. 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]

FT 1
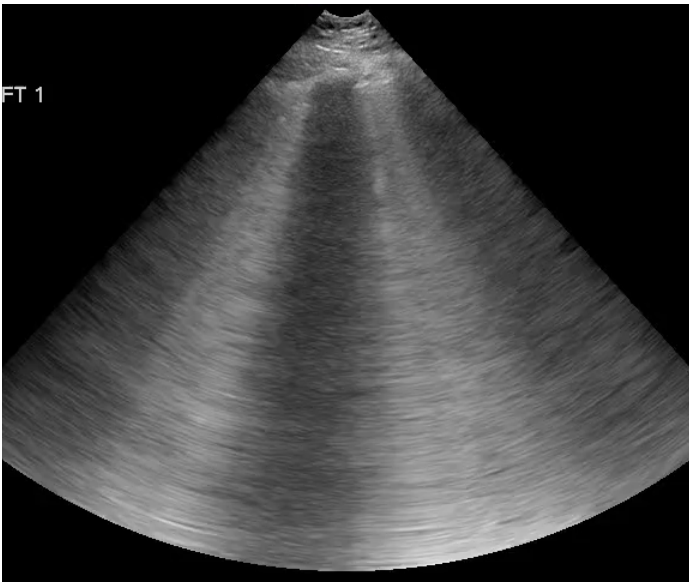
Lung (or pulmonary ultrasound) is one of the easiest ultrasound assessments to learn and perform. Even in patients with a high BMI, the lung can be evaluated. Additionally, lung ultrasound has high inter-rater agreement.

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.
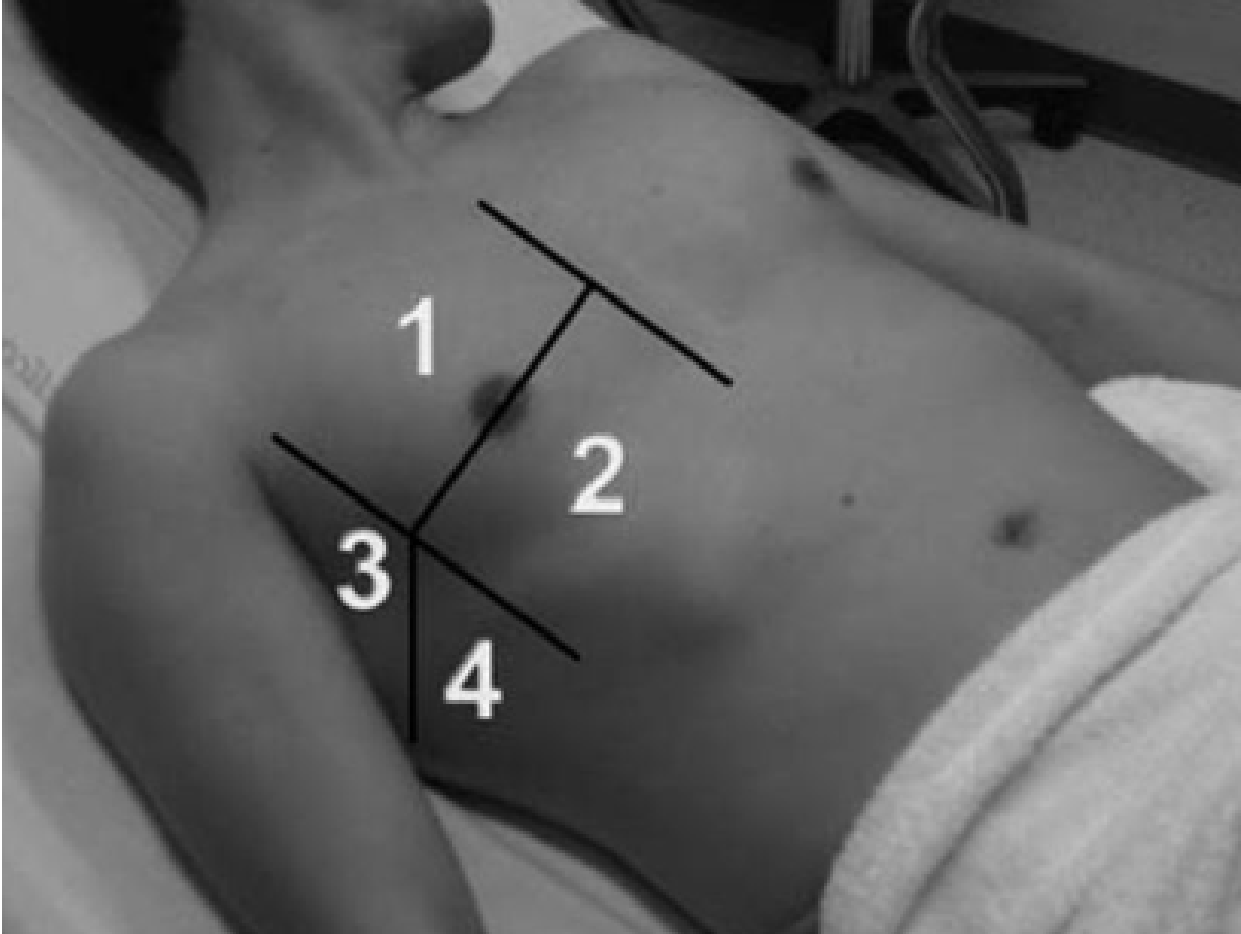
The eight zone protocol breaks each hemi-thorax into 4 zones, divided by the parasternal (PS) Line, Ant axillary line (AAL), posterior axillary line (PAL) and anatomic nipple line (ANL). In the clinical setting of suspected AHF, pulmonary edema is determined sonographically as greater than three B-lines 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.

<u>Machine settings</u>

- 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)
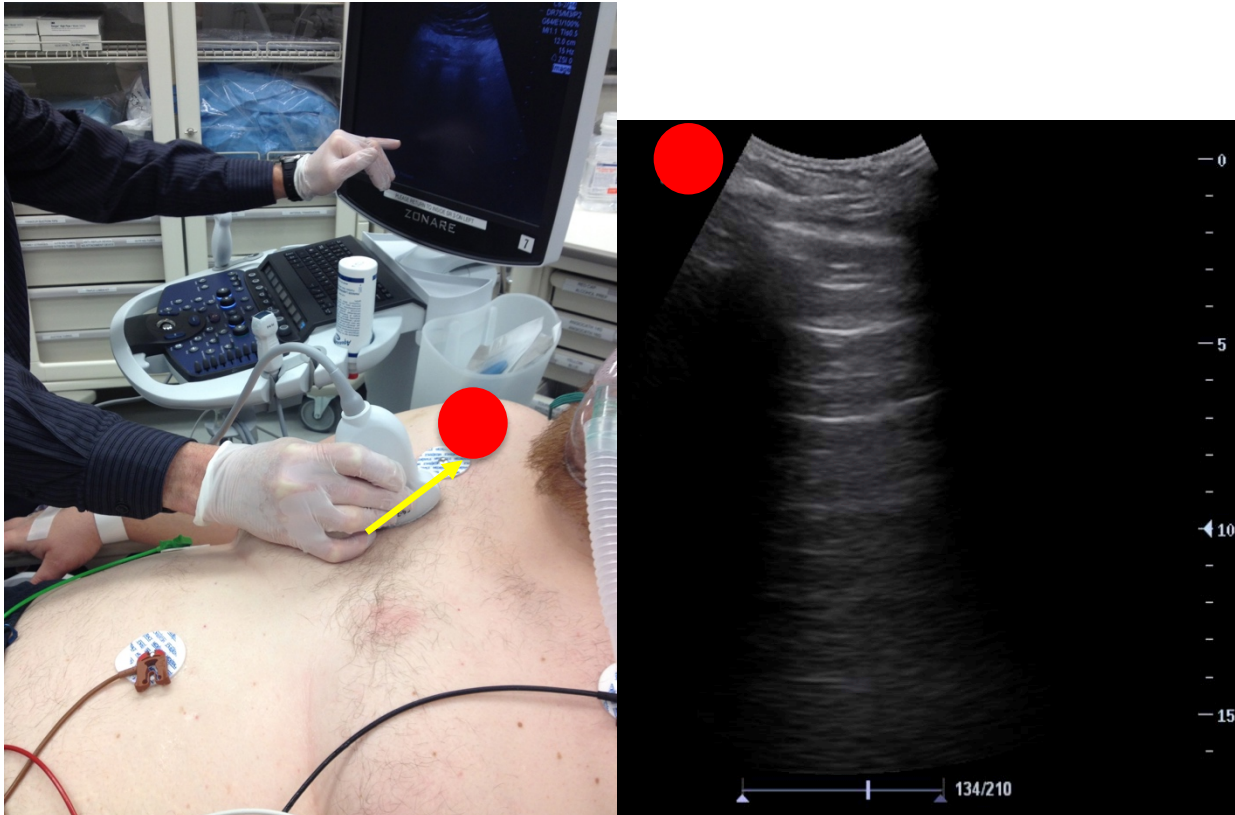

- Starting off on the **Right** in **Zone 1**: you want the indicator towards the patient's head. Identify ribs by shadowing and identify a rib space (see image below)
- Label R1
- Then turn 90 degrees with **indicator towards patient's right** so you are still in a rib space but the probe is **HORIZONTAL**
- 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
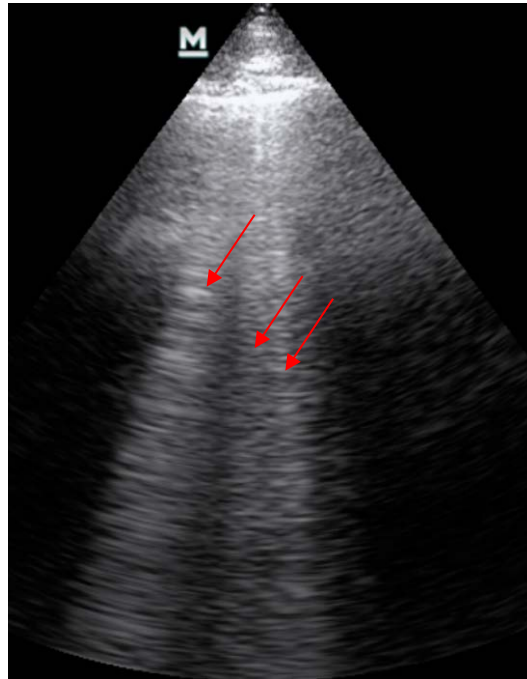
- B lines are vertical echogenic artifacts that originate from the pleural line and extend to the bottom of the ultrasound screen
- Below image is an example of how to count individual B lines

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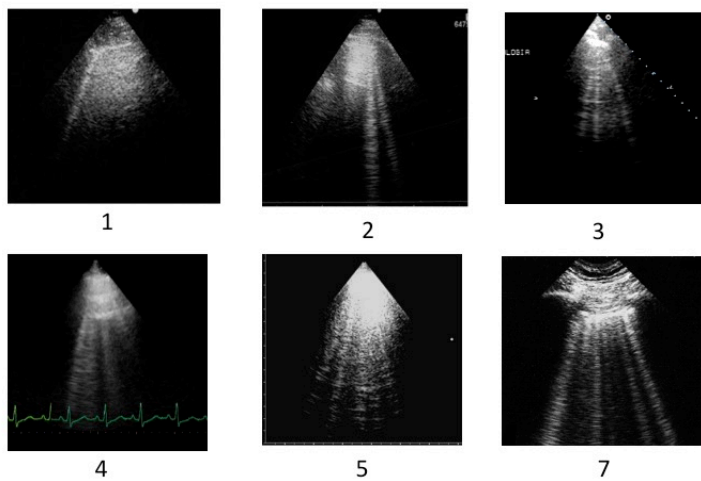
- In the situation where the whole footprint is 'white out' (see below image) count as 20 B lines
- The maximum number of B lines per sector is 20
- Count the maximum number of B lines you see
- If half of the footprint is a 'white out' count as 10 B lines
- Estimate percentage of white out
- Count up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

PLEURAL EFFUSION

- Document pleural effusion as yes or no
- Note the size (small, medium or large)
- If pleural effusion and no lung is seen in the zone = 0 B lines
- If pleural effusion and lung is seen = count number of B lines seen in lung

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.
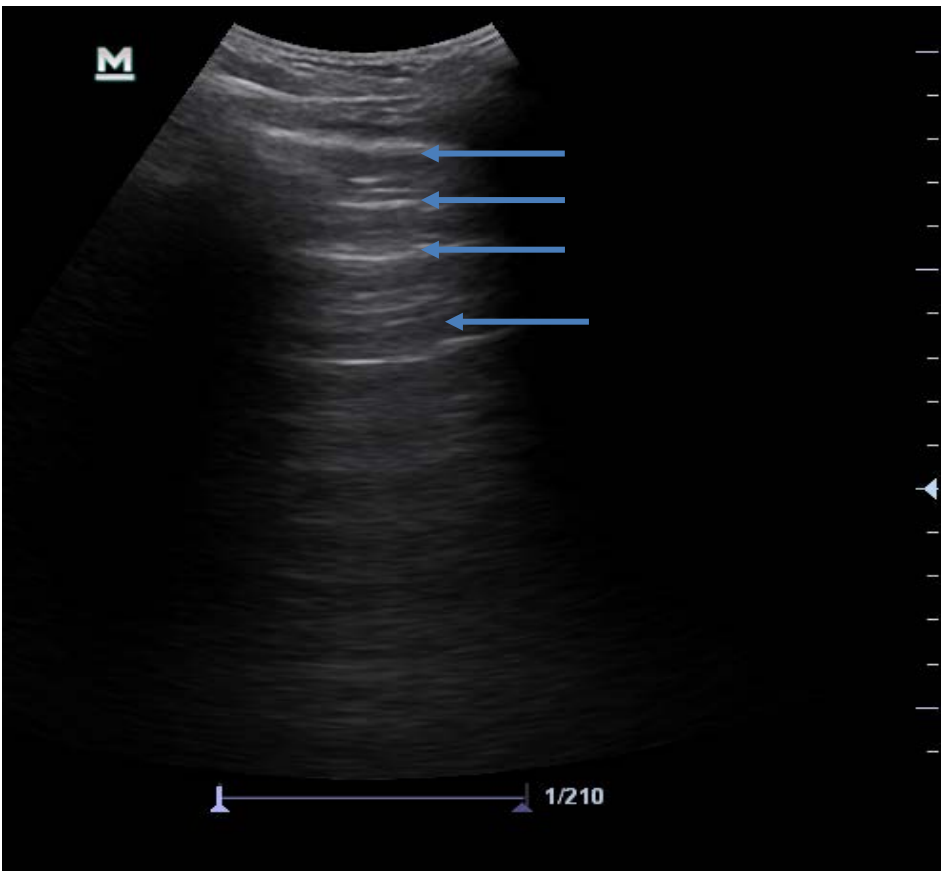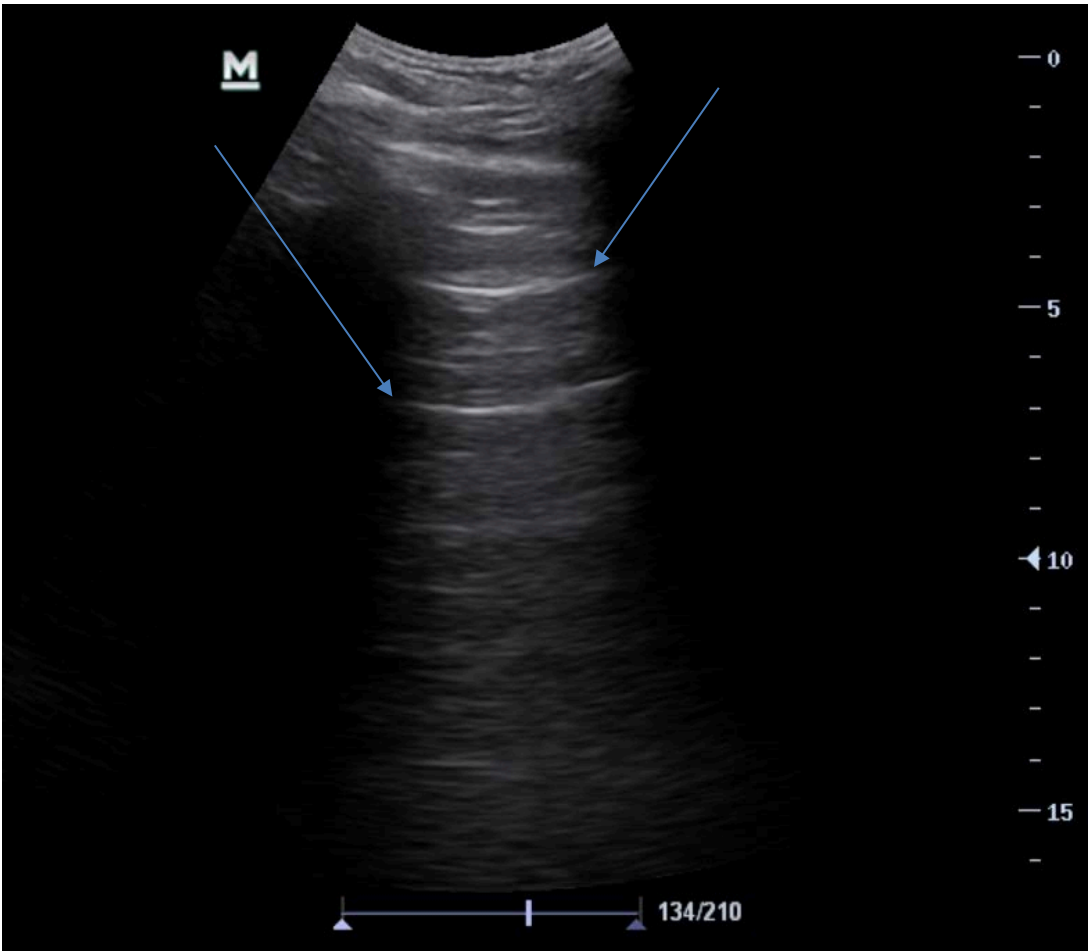
The figure below shows B lines. These are vertical echogenic artifacts that originate from the pleural line, extend to the bottom of the ultrasound screen.

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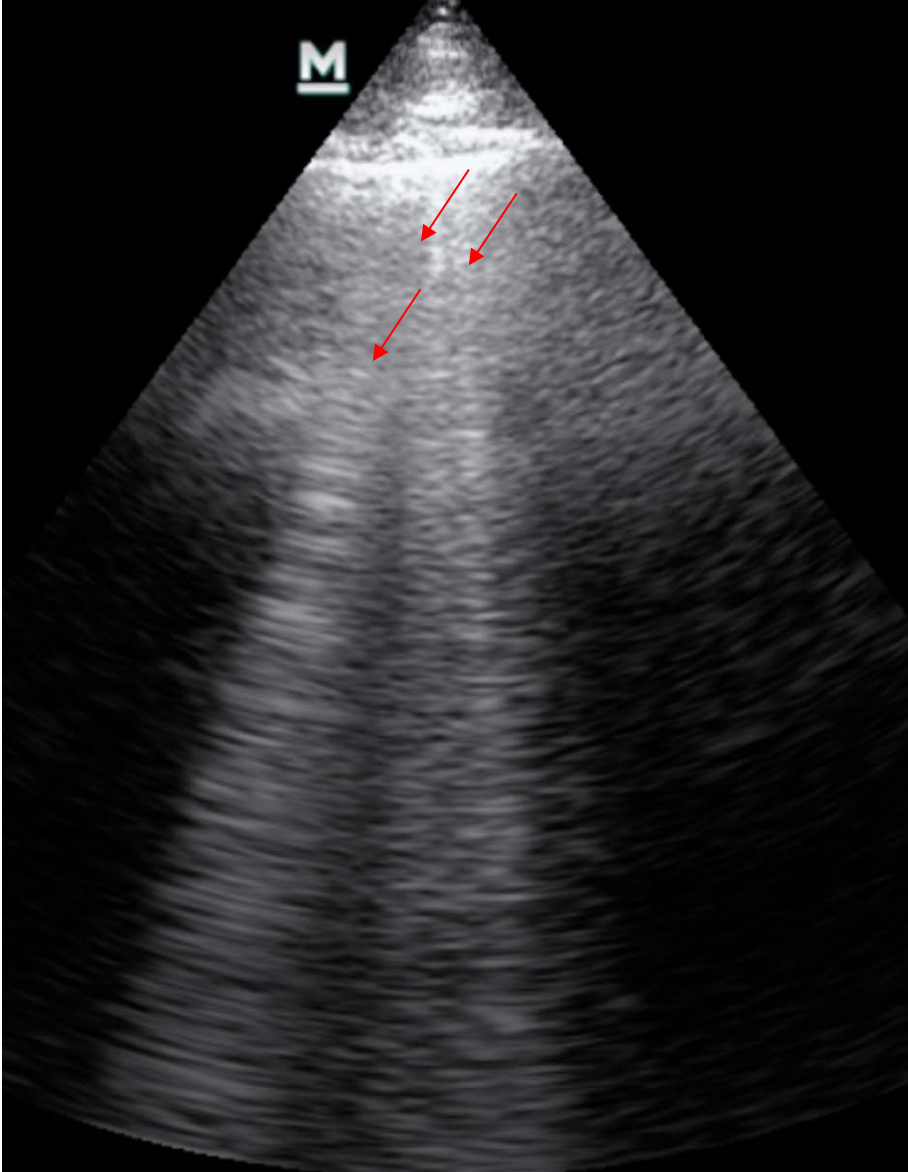
B lines may be seen outside of AHF. Clinical context is crucial! The table below shows other reasons why B lines may be present.

FOCAL	DIFFUSE
Infarct	Pulmonary Edema
Contusion	ARDS
Cancer	Pulmonary Fibrosis
Pneumonia/Pneumonitis	

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 are then 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 grade 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/time stamp, which may also be removed. Additional, non-identifiable labels will be added for study purposes. These will then be uploaded into BOX HEALTH.

Two BOX HEALTH 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 extra vascular lung water (EVLW). Past studies demonstrate correlation of B-line artifacts with the following: (1) natiuretic peptide levels, (2) invasive hemodynamics, (3) chest xray, (4) clinical assessments, and (5) computed tomography.[1-5] Moreover, B-lines may resolve after treatment.[6] 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 hopsitalization. (See Figure 1 – Trial design flow below)

Figure 1: Trial Schematic
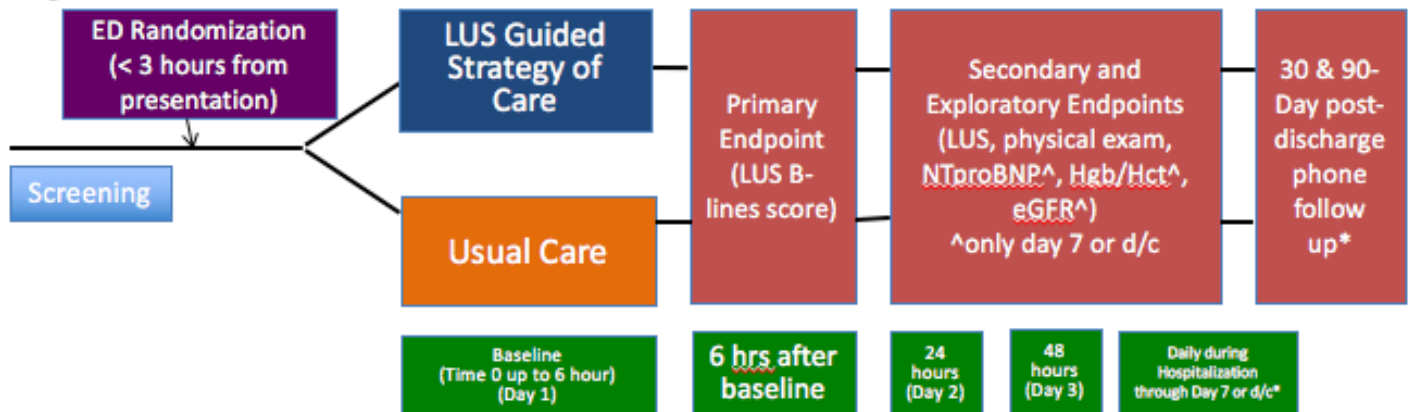
For diagnostic purposes, previously published protocols have been the most well-studied.

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 one 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 (anytime during day)
    - HD5: Day 5 (anytime during day)
    - HD6: Day 6 (anytime during day)
    - HD7: Day 7 (anytime during day)
- **If <u>standard care arm</u> 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 curivilinear or abdominal (2-5MHz) 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 visulization. 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-MHz abdominal probe and the setting is 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 (2-5MHz)

2) The depth will be set to 18cm

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 yields excellent correlation with expert sonographers.[40,48] 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 if initial review suggests 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.
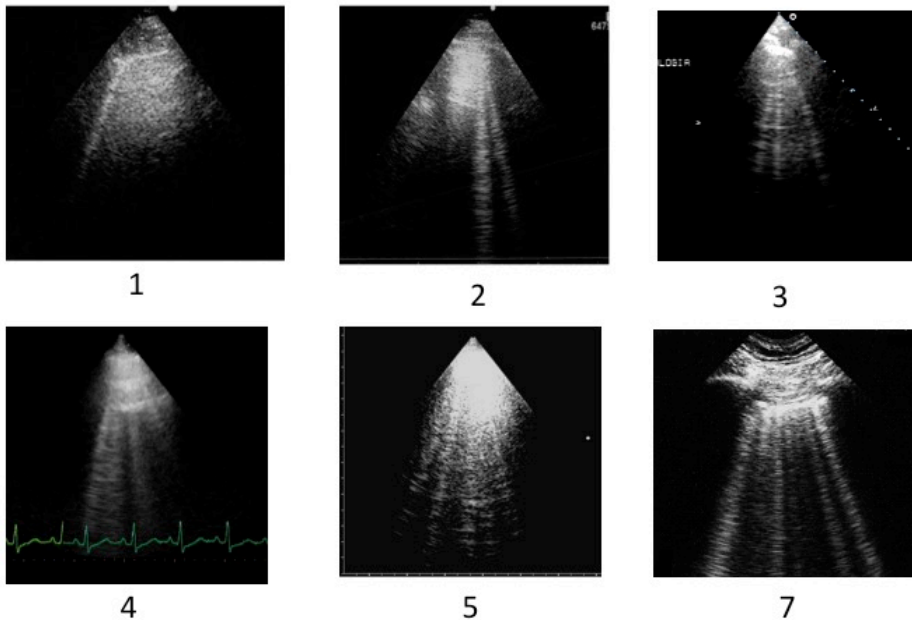
Figure 3: Counting of B-lines using Lung Ultrasound

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)

B lines will be counted as the number seen per acoustic windown.   See Figure 3.

In the situation where there is 'white out' or diffuse B lines in a rib space, this will be counted as 10 B-lines. Half the rib space will be 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 at the time of scan post-enrollment. For example, Scan 0 is at time of enrollment. Scan 24 is is 24 hours post-enrollment, Scan 72 is 72 hours post enrollment. All images will also be date/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 whited 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 de-identified, 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 failures of de-identification.   Furthermore, the Core Lab will not have access to any clinical information on the patient, further limiting the potential for clinical information to bias image interpretation. To minimize the potential bias of having a single sites images reviewed, images from one site will be mixed with other sites upon arrival at the Core Lab. 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 back up and secondary storage will occur on a daily basis

18   LITERATURE REFERENCES

1.   Alexander P, Alkhawam L, Curry J, et al. Lack of evidence for intravenous vasodilators in ED patients with acute heart failure: a systematic review. *Am J Emerg Med.* 2014.

2.   Collins SP, Levy PD, Lindsell CJ, et al. The rationale for an acute heart failure syndromes clinical trials network. *J Card Fail.* 2009;15(6):467-474.

3.   Collins SP, Lindsell CJ, Pang PS, et al. Bayesian adaptive trial design in acute heart failure syndromes: Moving beyond the mega trial. *Am Heart J.* 2012;164(2):138-145.

4.   Collins SP, Lindsell CJ, Storrow AB, et al. Early changes in clinical characteristics after emergency department therapy for acute heart failure syndromes: identifying patients who do not respond to standard therapy. *Heart Fail Rev.* 2012;17(3):387-394.

5.   Collins SP, Storrow AB, Levy PD, et al. Early management of patients with acute heart failure: state of the art and future directions--a consensus document from the SAEM/HFSA acute heart failure working group. *Acad Emerg Med.* 2015;22(1):94-112.

6.   Felker GM, Butler J, Collins SP, et al. Heart Failure Therapeutics on the Basis of a Biased Ligand of the Angiotensin-2 Type 1 Receptor: Rationale and Design of the BLAST-AHF Study (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure). *JACC Heart failure.* 2015.

7.   Heart Failure Executive C, Peacock WF, Fonarow GC, et al. Society of Chest Pain Centers Recommendations for the evaluation and management of the observation stay acute heart failure patient: a report from the Society of Chest Pain Centers Acute Heart Failure Committee. *Critical pathways in cardiology.* 2008;7(2):83-86.

8.   Pang PS, Collins SP, Miro O, et al. The role of the emergency department in the management of acute heart failure: An international perspective on education and research. *Eur Heart J Acute Cardiovasc Care.* 2015.

9.   Peacock WF, Braunwald E, Abraham W, et al. National Heart, Lung, and Blood Institute working group on emergency department management of acute heart failure: research challenges and opportunities. *J Am Coll Cardiol.* 2010;56(5):343-351.

10.   Peacock WF, Fonarow GC, Ander DS, et al. Society of Chest Pain Centers recommendations for the evaluation and management of the observation stay acute heart failure patient-parts 1-6. *Acute cardiac care.* 2009;11(1):3-42.

11.   Storrow AB, Lindsell CJ, Collins SP, et al. Standardized reporting criteria for studies evaluating suspected acute heart failure syndromes in the emergency department. *Journal of the American College of Cardiology.* 2012;60(9):822-832.

12.   Weintraub NL, Collins SP, Pang PS, et al. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. *Circulation.* 2010;122(19):1975-1996.

13.   Collins SP, Pang PS, Butler J, Fonarow G, Metra M, Gheorghiade M. Revisiting cardiac injury during acute heart failure: further characterization and a possible target for therapy. *Am J Cardiol.* 2015;115(1):141-146.

14.   Pang PS, Collins SP, Sauser K, et al. Assessment of dyspnea early in acute heart failure: patient characteristics and response differences between likert and visual analog scales. *Acad Emerg Med.* 2014;21(6):659-666.

15.   Pang PS, Collins SP, Maisel A, Jesse R. Reply to: Decision algorithms are needed in acute heart failure in the emergency department. *J Card Fail.* 2013;19(2):147-148.

16.   Collins SP, Pang PS, Fonarow GC, Yancy CW, Bonow RO, Gheorghiade M. Is hospital admission for heart failure really necessary?: the role of the emergency department and observation unit in preventing hospitalization and rehospitalization. *J Am Coll Cardiol.* 2013;61(2):121-126.

17.   Pang PS, Jesse R, Collins SP, Maisel A. Patients with acute heart failure in the emergency department: do they all need to be admitted? *J Card Fail.* 2012;18(12):900-903.

18.   Pang PS, Collins SP, Storrow AB. Letter by Pang et al regarding article, "Early deaths in heart failure patients discharged from the emergency department: a population-based analysis". *Circulation Heart failure.* 2010;3(4):e22; author reply e23.

19.   Mebazaa A, Pang PS, Tavares M, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. *Eur Heart J.* 2010;31(7):832-841.

20.   Collins SP, Pang PS, Lindsell CJ, et al. International variations in the clinical, diagnostic, and treatment characteristics of emergency department patients with acute heart failure syndromes. *Eur J Heart Fail.* 2010;12(11):1253-1260.

21.   Pang PS, Tavares M, Collins SP, et al. Design and rationale of the URGENT Dyspnea study: an international, multicenter, prospective study. *American journal of therapeutics.* 2008;15(4):299-303.

22.   Pang PS, Cleland JG, Teerlink JR, et al. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. *Eur Heart J.* 2008;29(6):816-824.

23.   Collins S, Storrow AB, Kirk JD, Pang PS, Diercks DB, Gheorghiade M. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. *Annals of emergency medicine.* 2008;51(1):45-57.

24.   Pang PS, Levy P, Shah SJ. Treatment of acute heart failure in the emergency department. *Expert review of cardiovascular therapy.* 2013;11(9):1195-1209.

25.   Eapen ZJ, Liang L, Fonarow GC, et al. Validated, electronic health record deployable prediction models for assessing patient risk of 30-day rehospitalization and mortality in older heart failure patients. *JACC Heart failure.* 2013;1(3):245-251.

26.   Dharmarajan K, Hsieh AF, Kulkarni VT, et al. Trajectories of risk after hospitalization for heart failure, acute myocardial infarction, or pneumonia: retrospective cohort study. *BMJ.* 2015;350:h411.

27.   Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *International journal of cardiology.* 2014;171(3):368-376.

28.   Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med.* 2009;360(14):1418-1428.

29.   Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. *JAMA : the journal of the American Medical Association.* 2010;303(21):2141-2147.

30.   Ross JS, Chen J, Lin Z, et al. Recent national trends in readmission rates after heart failure hospitalization. *Circulation Heart failure.* 2010;3(1):97-103.

31.   Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol.* 2013;61(4):391-403.

32.   Maisel AS, Peacock WF, McMullin N, et al. Timing of immunoreactive B-type natriuretic peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. *J Am Coll Cardiol.* 2008;52(7):534-540.

33.   Wong YW, Fonarow GC, Mi X, et al. Early intravenous heart failure therapy and outcomes among older patients hospitalized for acute decompensated heart failure: findings from the Acute Decompensated Heart Failure Registry Emergency Module (ADHERE-EM). *Am Heart J.* 2013;166(2):349-356.

34.   Ramirez A, Abelmann WH. Cardiac decompensation. *New Eng J Med.* 1974;290:499-501.

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.

36.   Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Association. *Circulation.* 2014.

37.   Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013.

38.   Gheorghiade M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *The American journal of medicine.* 2006;119(12 Suppl 1):S3-S10.

39.   Gheorghiade M, Follath F, Ponikowski P, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail.* 2010;12(5):423-433.

40.   O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail.* 2005;11(3):200-205.

41.   Mentz RJ, Kjeldsen K, Rossi GP, et al. Decongestion in acute heart failure. *Eur J Heart Fail.* 2014;16(5):471-482.

42.   Silvers SM, Howell JM, Kosowsky JM, Rokos IC, Jagoda AS, American College of Emergency P. Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. *Annals of emergency medicine.* 2007;49(5):627-669.

43.   Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J.* 2000;140(6):840-847.

44.   Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J.* 2013;34(11):835-843.

45.   Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* 2004;291(16):1963-1971.

46.   Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *The New England journal of medicine.* 2001;345(8):574-581.

47.   Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol.* 2003;41(10):1797-1804.

48.   Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. *Circulation Heart failure.* 2013;6(2):240-245.

49.   Yancy CW, Fonarow GC. Quality of care and outcomes in acute decompensated heart failure: The ADHERE Registry. *Curr Heart Fail Rep.* 2004;1(3):121-128.

50.   Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation.* 2010;122(3):265-272.

51.   Flint KM, Allen LA, Pham M, Heidenreich PA. B-type natriuretic peptide predicts 30-day readmission for heart failure but not readmission for other causes. *Journal of the American Heart Association.* 2014;3(3):e000806.

52.   Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circulation Heart failure.* 2012;5(1):54-62.

53.   Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA : the journal of the American Medical Association.* 1989;261(6):884-888.

54.   Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA : the journal of the American Medical Association.* 2005;294(15):1944-1956.

55.   Storrow AB, Jenkins CA, Self WH, et al. The burden of acute heart failure on U.S. emergency departments. *JACC Heart failure.* 2014;2(3):269-277.

56.   Schuur JD, Venkatesh AK. The growing role of emergency departments in hospital admissions. *The New England journal of medicine.* 2012;367(5):391-393.

57.   Gargani L. Lung ultrasound: a new tool for the cardiologist. *Cardiovasc Ultrasound.* 2011;9:6.

58.   Picano E, Gargani L. Ultrasound lung comets: the shape of lung water. *Eur J Heart Fail.* 2012;14(11):1194-1196.

59.   Lichtenstein D, Meziere G, Biderman P, Gepner A, Barre O. The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. *Am J Respir Crit Care Med.* 1997;156(5):1640-1646.

60.   Picano E, Frassi F, Agricola E, Gligorova S, Gargani L, Mottola G. Ultrasound lung comets: a clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr.* 2006;19(3):356-363.

61.   Martindale JL. Diagnosing Acute Heart Failure in the Emergency Department. *Acad Emerg Med.* 2016.

62.   Martindale JL, Noble VE, Liteplo A. Diagnosing pulmonary edema: lung ultrasound versus chest radiography. *European journal of emergency medicine : official journal of the European Society for Emergency Medicine.* 2013;20(5):356-360.

63.   Bedetti G, Gargani L, Corbisiero A, Frassi F, Poggianti E, Mottola G. Evaluation of ultrasound lung comets by hand-held echocardiography. *Cardiovasc Ultrasound.* 2006;4:34.

64.   Jambrik Z, Monti S, Coppola V, et al. Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. *Am J Cardiol.* 2004;93(10):1265-1270.

65.   Mallamaci F, Benedetto FA, Tripepi R, et al. Detection of pulmonary congestion by chest ultrasound in dialysis patients. *JACC Cardiovasc Imaging.* 2010;3(6):586-594.

66.   Basso F, Milan Manani S, Cruz DN, et al. Comparison and Reproducibility of Techniques for Fluid Status Assessment in Chronic Hemodialysis Patients. *Cardiorenal medicine.* 2013;3(2):104-112.

67.   Pivetta E, Goffi A, Lupia E, et al. Lung Ultrasound-Implemented Diagnosis of Acute Decompensated Heart Failure in the ED: A SIMEU Multicenter Study. *Chest.* 2015;148(1):202-210.

68.   Gargani L, Pang PS, Frassi F, et al. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: a lung ultrasound study. *Cardiovasc Ultrasound.* 2015;13:40.

69.   Miglioranza MH, Gargani L, Sant'Anna RT, et al. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc Imaging.* 2013;6(11):1141-1151.

70.   Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med.* 2012;38(4):577-591.

71.   Neskovic AN, Edvardsen T, Galderisi M, et al. Focus cardiac ultrasound: the European Association of Cardiovascular Imaging viewpoint. *European heart journal cardiovascular Imaging.* 2014;15(9):956-960.

72.   Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine--short version. *Eur Heart J.* 2015;36(30):1958-1966.

73.   Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016.

74.   Noble VE, Murray AF, Capp R, Sylvia-Reardon MH, Steele DJ, Liteplo A. Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. *Chest.* 2009;135(6):1433-1439.

75.   Coiro S, Rossignol P, Ambrosio G, et al. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail.* 2015;17(11):1172-1181.

76.   Gargani L, Pang PS, Frassi F, et al. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: a lung ultrasound study. *Cardiovasc Ultrasound.* 2015;13(1):40.

77.   Cogliati C, Casazza G, Ceriani E, et al. Lung ultrasound and short-term prognosis in heart failure patients. *International journal of cardiology.* 2016;218:104-108.

78.   Cibinel GA, Casoli G, Elia F, et al. Diagnostic accuracy and reproducibility of pleural and lung ultrasound in discriminating cardiogenic causes of acute dyspnea in the emergency department. *Intern Emerg Med.* 2012;7(1):65-70.

79.   Noble VE, Lamhaut L, Capp R, et al. Evaluation of a thoracic ultrasound training module for the detection of pneumothorax and pulmonary edema by prehospital physician care providers. *BMC medical education.* 2009;9:3.

80.   Baker K, Soong L, Harding T, et al. Sensitivity, specificity and diagnostic accuracy of novices integrating lung ultrasound into the care of breathless older patients. *Australas J Ultrasound Med.* 2015;18(4):143-145.

81.   Brattain LJ, Telfer BA, Liteplo AS, Noble VE. Automated B-line scoring on thoracic sonography. *J Ultrasound Med.*
        2013;32(12):2185-2190.

82.   Platz E, Pivetta E, Merz AA, Peck J, Rivero J, Cheng S. Impact of device selection and clip duration on lung ultrasound
        assessment in patients with heart failure. *Am J Emerg Med.* 2015.

83.   Platz E, Lewis EF, Uno H, et al. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory
        heart failure patients. *Eur Heart J.* 2016;37(15):1244-1251.

84.   Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute
        decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol.*
        2013;62(6):516-524.

85.   Logeart D, Thabut G, Jourdain P, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of
        re-admission after decompensated heart failure. *J Am Coll Cardiol.* 2004;43(4):635-641.

86.   Felker GM, Pang PS, Adams KF, et al. Clinical trials of pharmacological therapies in acute heart failure syndromes: lessons
        learned and directions forward. *Circulation Heart failure.* 2010;3(2):314-325.

87.   Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events
        in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data
        Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol.* 2015;66(4):403-469.

88.   Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts
        outcome after hospital discharge in heart failure patients. *Circulation.* 2004;110(15):2168-2174.

89.   Stienen S, Salah K, Dickhoff C, et al. N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) Measurements Until a 30%
        Reduction Is Attained During Acute Decompensated Heart Failure Admissions and Comparison With Discharge NT-proBNP
        Levels: Implications for In-Hospital Guidance of Treatment. *J Card Fail.* 2015.

90.   Stienen S, Salah K, Moons AH, et al. Rationale and design of PRIMA II: A multicenter, randomized clinical trial to study the
        impact of in-hospital guidance for acute decompensated heart failure treatment by a predefined NT-PRoBNP target on the
        reduction of readmIssion and Mortality rAtes. *Am Heart J.* 2014;168(1):30-36.

91.   Efron B, Tibshirani R. *An Introduction to the Bootstrap.* Boca Raton: Chapman & Hall/CRC; 1993.

92.   Breiman L, Friedman JH, Stone CJ. *Classification and Regression Trees.* London: Chapman & Hall; 1984.

93.   Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from
        area under the ROC curve to reclassification and beyond. *Statistics in medicine.* 2008;27(2):157-172; discussion 207-112.

94.   Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure
        usefulness of new biomarkers. *Statistics in medicine.* 2011;30(1):11-21.

95.   Shen C, Weissfeld L. Application of pattern-mixture models to outcomes that are potentially missing not at random using
        pseudo maximum likelihood estimation. *Biostatistics.* 2005;6(2):333-347.

96.   Rubin D. Multiple imputation after 18+ years. *Journal of the American Statistical Association.* 1996;91:473-489.

97.   Shen C, Weissfeld L. A copula model for repeated measurements with non-ignorable non-monotone missing outcome. *Stat
        Med.* 2006;25(14):2427-2440.

98.   Shen C, Gao S. A mixed-effects model for cognitive decline with non-monotone non-response from a two-phase longitudinal study of dementia. *Stat Med.* 2007;26(2):409-425.