"Nitroglycerin vs. Furosemide using Lung Ultrasound Pilot Trial" (N-FURIOUS)

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IND/IDE Sponsor: N/A

Funded by: American Heart Association

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ClinicalTrials.gov Identifier: NCT03259165

Summary of Changes Amendment A012

1. *Changes to eligibility criteria*
2. *Updated treatment algorithm*
3. *Clarification of timing of dyspnea assessments*

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: _____

_____

Institution Address: _____

_____

_____

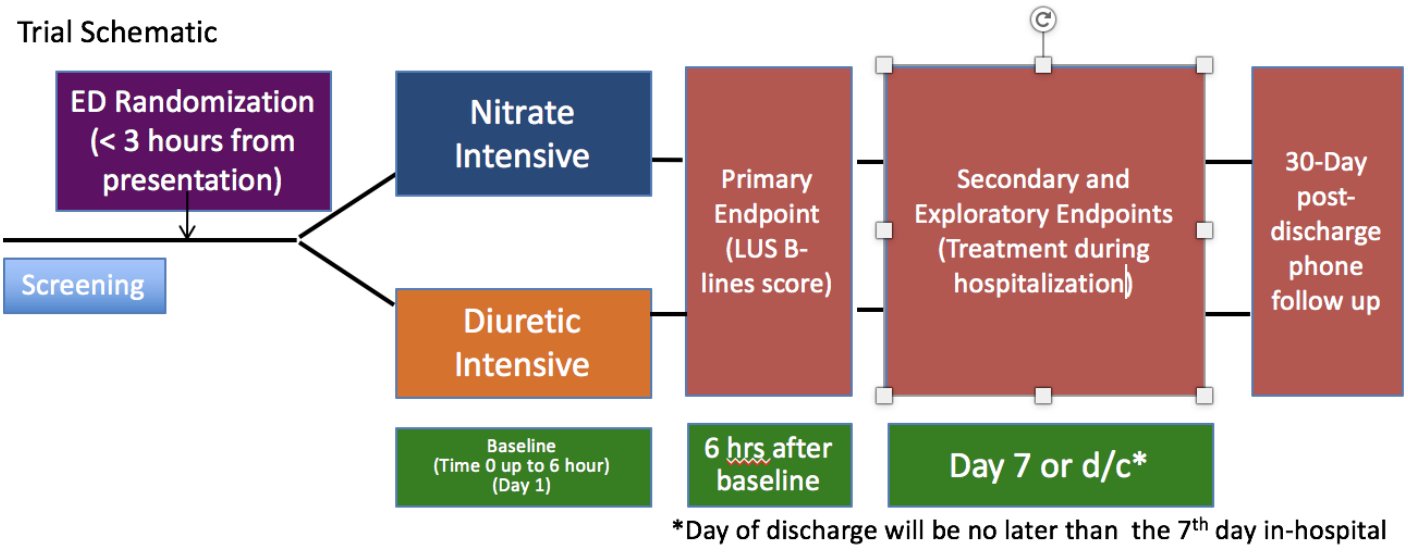
Signature: _____ Date: _____

PROTOCOL SUMMARY

Title:	***"Nitroglycerin vs. Furosemide using Lung Ultrasound Pilot Trial" (N-FURIOUS)***
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 two-site, randomized controlled design, this pilot study will test whether a nitrate intense strategy more effectively reduces congestion, defined by LUS B-lines, better than a diuretic intense strategy.
Objectives:	**1**: To determine whether a nitrate intense strategy safely reduces congestion, defined by LUS B-lines, better than a diuretic intense strategy. **2.** To demonstrate feasibility of recruitment and compliance with study protocol to inform future study design and enrollment projections, an external site will also test our study protocol.
Endpoint	A comparison of total B-lines 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 during their ED visit within 3 hours of presentation.
Phase:	2
Number of Sites enrolling participants:	Two sites (3 total hospitals). Projected sample size, n=70.
Description of Study Agent:	Nitrate intense vs. Diuretic intense AHF treatment strategy
Study Duration:	2 years. There will be three months of start up, and one month of study conclusion work. Enrollment will occur over 20 months, which equals 3.5 patients month. As there will be staggered start up to determine replication, approximately 1-2 patients/month.
Participant Duration:	30 days post discharge

SCHEMATIC OF STUDY DESIGN



*whichever comes first

**Presentation is definied as first time recorded when placed in a room to be treated. This allows patients to still be enrolled despite a long waiting room time

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).

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.

Xiaochun Li PhD, from the Department of Biostatistics at Indiana University will lead the data core.

Sean Collins MD (Vanderbilt University), Vice-Chair of Research, will be 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.

Luna Gargani MD is an Assistant Professor of Cardiology at the University of Pisa. She will direct the core imaging lab.

In her role, she will only see blinded images; never any patient identifiable information.

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] Despite this crucial starting role, **ED AHF pharmacological management today is largely the 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] <u>There remains a critical unmet need for evidence based ED AHF management.</u>

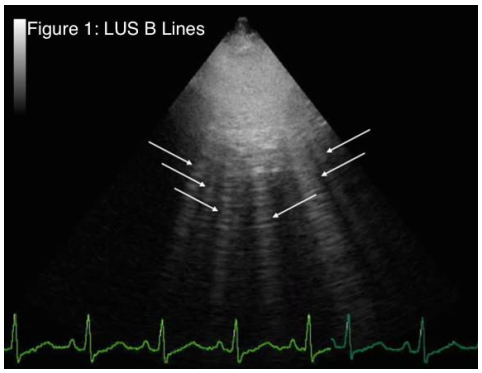
2.2 RATIONALE

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]



Initial Therapy

IV loop diuretics are the mainstay of AHF management. Yet emergency physicians are often reluctant to use IV loop diuretics, largely influenced by small studies and retrospective studies suggesting an association with harm. Nitrates are either recommended above diuretics or even to replace diuretics in popular blogs, podcasts, or online forums. Arguably, neither IV loop diuretics nor nitrates have definitive outcome data regarding efficacy or harm. This is evident in guidelines, where IV loop diuretics receive a class I, B indication, and nitrates a IIb, A recommendation. The evidence that does exist supports their use. Whether one should be used before another, both, how to combine them, and in whom, is not well defined.

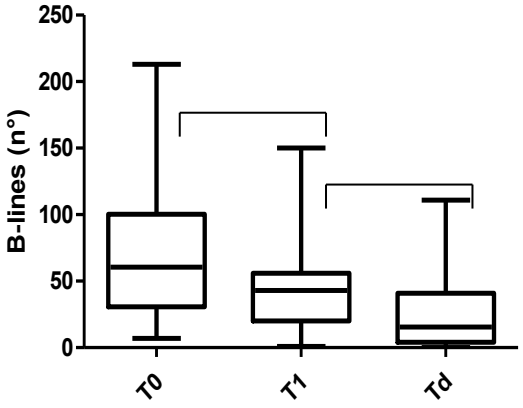
Lung Ultrasound as an Endpoint

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.

Figure 2



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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. 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 or when one therapy (nitrates or diuretics) are used initially over the other. To mitigate these risks, this study is being conducted in an ED setting, where ICU level care is routinely provided. If needed, rescue therapy with either drug (or additional therapies) may be provided.

For IV loop diuretics, commonly encountered risks include potential acute kidney injury (AKI) and over diuresis leading to hypovolemia which can lead to circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients. Electrolyte depletion may also occur especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids, ACTH, licorice in large amounts, or prolonged use of laxatives. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects. 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, there will be no pre-discharge lab draw. 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. Marked sensitivity to the hypotensive effects of nitrates (manifested by nausea, vomiting, weakness, diaphoresis, pallor and collapse) may occur at therapeutic doses. Syncope due to nitrate vasodilation has been reported. Vertigo, weakness, palpitation and other manifestations of postural hypotension may

develop occasionally, particularly in erect, immobile patients. 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 may be severe and persistent may occur immediately after use. This will be treated with Tylenol or other non-narcotic analgesic medication. Nitroglycerin may produce a burning or tingling sensation when administered sublingually. Flushing, drug rash, and exfoliative dermatitis have also been reported in patients receiving nitrate therapy.

Potential Risks from Ultrasound: There are almost no risks to the use of ultrasound. Ultrasound is what is currently used to visualize the fetus in pregnant patients. The same type of ultrasound will be used for this study. There is NO radiation involved. The biggest complaint from use of ultrasound is the gel placed on the probe or body to improve visualization of the US waves is often cold.

2.3.2 KNOWN POTENTIAL BENEFITS

Patients enrolled in this study may receive a benefit such as feeling better faster. If the study shows that a nitrate or furosemide first strategy leads to faster resolution of congestion, future studies may explore early treatment in more detail. If either strategy 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 nitrate intense strategy safely reduces congestion, defined by LUS B-lines, better than a diuretic intense strategy.

2. To demonstrate feasibility of recruitment and compliance with study protocol to inform future study design and enrollment projections, an external site will also test our study protocol.

Purpose:

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

Hypothesis 1a: Nitrate intense treated patients will have less congestion, defined by LUS B-lines, than diuretic intense patients at 6 hours after start of treatment.

Hypothesis 1b: Nitrate intense treated patients will have greater dyspnea relief then diuretic intense patients at 6 hours after start of treatment.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

A two-site, prospective, randomized, pilot trial comparing a nitrate intense vs. diuretic intense strategy. 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. 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 either study arm. For randomized patients, study protocol will continue until there is a decrease in B-

lines to ≤ 15 or 6 hours of care has been delivered. Subjects who are hospitalized prior to the completion of the 6 hour protocol may continue on the protocol until the six hour treatment window is concluded. 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.

4.2.1 PRIMARY ENDPOINT

The total number of B-lines at the conclusion of ED AHF management

Main Secondary Endpoints:

Dyspnea will also be assessed using a 5-point and 7-point Likert scale.

B-lines <= 15 at the conclusion of ED AHF management

4.2.2 EXPLORATORY ENDPOINTS

The following table lists the exploratory endpoints

Table 3: Exploratory Endpoints	
Total DAOOH through 30 days post-discharge	Association of B-lines at discharge and 30 day outcomes
Time to reach B-lines ≤15	Association of baseline, discharge, and change of b-lines with 30 day outcomes
Change in physical exam findings	All Cause readmissions, All cause ED re-visits

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

v. BNP > 500pg/mL

5.2 PARTICIPANT EXCLUSION CRITERIA

1) Chronic renal dysfunction, including ESRD or eGFR < 20ml//min/1.73m^2.

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

3) SBP < 120

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

12) Severe valvular disease

13) Anuria

14) Allergy or hypersensitivity to nitroglycerin, furosemide or sulfa

15) Concern for cardiac tamponade or restrictive cardiomyopathy

16) Elevated intracranial pressure

17) Recent use of PDE5 inhibitors

It is important to note that AHF is a clinical diagnosis. In other words, there is no test or image that 100% conclusively demonstrates a patient does or does not have AHF. In most studies, 2 cardiologists who independently review the chart and agree its heart failure set the 'gold standard.' Thus, there will inevitably be instances where the ER will diagnose AHF and be wrong and vice-versa. From a clinical standpoint however, patients are cared for based on their presumptive diagnosis. Thus, instances where the ER diagnoses AHF and then the inpatient teams confirm an alternative diagnosis would NOT violate the spirit or actual intent of the study protocol.

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 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.

Patients may be enrolled at anytime during their ED stay, but preferably within 3 hours of first placement in a room in the emergency department. Time spent in the waiting room will not count towards these 3 hours.

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.

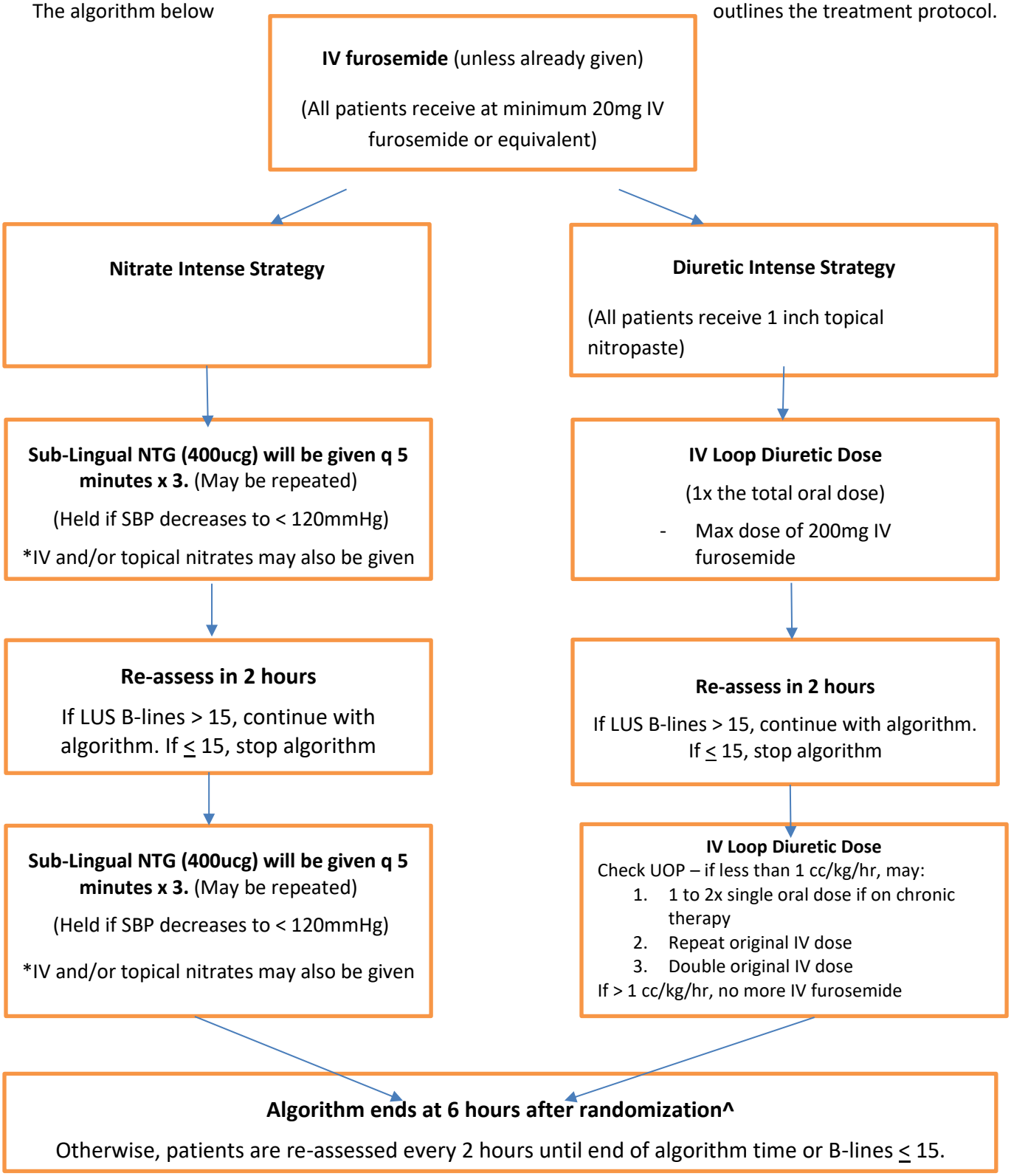
6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

This study will test a nitrate intense vs. diuretic intense early AHF strategy. No investigational therapies will be used. 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.



^the protocol was designed to be an ED based protocol. Thus, for patients who leave the ER prior to 6 hours, deviations from the algorithm will NOT be protocol violations.

** ALL enrolled patients will be re-assessed at least twice during their ED stay, unless the patient is discharged from the ER or other clinical priority. 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 from the ER or at 6 hours after start of treatment. IF the pre-discharge assessment is missed in the ER, if possible, this should occurs ASAP after arrival to the hospital floor, unless completed within one hour of the last assessment.

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

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: The protocol is not optional by the clinical team. 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.

NOTE: Urine output: An estimated urine output is acceptable.

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.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

The table below in section 7.3.4 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 followed during hospitalization, with at least one LUS performed within 48 hours of randomization. (Later than this window, but no more than 96 hours, is at the discretion of the site PI)

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 will be drawn for study purposes.

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.

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.

Patients may be enrolled at anytime during their ED stay, but preferably within 3 hours of first placement in a room in the emergency department. Time spent in the waiting room will not count towards these 3 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 eligibility criteria will be randomized. In regards to the SBP; a single recording below 120mmHg does NOT disqualify the patient as long as the SBP returns > 120mmHg. Randomization will occur via central IWRS system.

7.3.3 FOLLOW-UP & FINAL STUDY VISIT

Patients will be followed for a maximum of 30 days post-discharge. There will be NO further in-person visits once discharged. Patients will be called however at 30 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.

7.3.4 SCHEDULE OF EVENTS TABLE

Schedule of Events	Screening	Day 1 T00	Day 1 T02-04	Day 1 T06	Day 2-6 T24-D6	30 day follow up
Informed consent (I/E)	X					
Medical History	X					
Medication history	X					
Clinical Assessment[#]		X	X	X	X	
Body Weight, height, Vital Signs	ED SOC	VS only	VS only	VS only	BW/VS only	
5-point and 7-point Likert scale		X		X	X	
Labs: Electrolytes, hematology, NP, eGFR, Troponin	ED SOC					
12-lead ECG	ED SOC					
CXR	ED SOC					
LUS B-lines 8 zone	X (LUS T00)		X	X	X^^	
Nitrate vs. Diuretic intense management		X	X	X		
Lab draw: eGFR, Hgb/Hct^		X				
eCRF/data collection/verification		X				X
Assessment of AE/SAE's						X
Phone follow-up Vital Status						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 ^^ LUS to be performed up to 48 hours after hospitalization. If an obs unit patient, prior to discharge.

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]

- 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)
- T48: up to 48 hours after initial scan (Day 3) (+/- 12 hours)

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

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

8.1 SPECIFICATION OF SAFETY PARAMETERS

Mortality, re-hospitalization, and ED visits through 30 days will be assessed for safety as well as efficacy

Hypotension, defined as a SBP < 100mmHg or decrease > 60mmHg from baseline, 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 the follow up 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

• 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 EITHER STRATEGY OF CARE

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 5 days after ending study treatment. Patients will be followed for 30 days for ED visits, re-hospitalization, and mortality. 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 team

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, the IRB will be informed within 72 hours.

8.5 STUDY HALTING RULES

As a small pilot study, there are no formal stopping rules.

8.6 SAFETY OVERSIGHT

The PIs will be monitoring the study continuously throughout the study.

A monitoring check will be performed at 50% enrollment (35 patients) and the following will be reviewed:

1. Mortality
2. Re-hospitalizations
3. ICU utilization
4. NIV and intubation
5. Kidney function closest to discharge

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.

10.2 STATISTICAL HYPOTHESES

- *Hypothesis 1a: Nitrate intense treated patients will have less congestion, defined by LUS B-lines, than diuretic intense patients at 6 hours after start of treatment.*
- *Hypothesis 1b: Nitrate intense treated patients will have greater dyspnea relief then diuretic intense patients at 6 hours after start of treatment.*
- *Hypothesis 2: Each site (n=3) will enroll ~2 patient per month for 12 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

As a small, exploratory, pilot study, we are uncertain the difference, if any, between the two arms in regards to B-lines after treatment. 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 total number of B-lines at the conclusion of ED AHF management

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.

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. 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.

ANALYSIS OF THE SECONDARY ENDPOINTS

1. Dyspnea will also be assessed using a 5-point and 7-point Likert scale.

Dyspnea will be assessed at the baseline and 6 hours later (or closest time point prior to ER discharge using two instruments. Dyspnea will also be assessed at any time between D2 and D/C. A 7-point Likert scale to determine change from baseline: 1) markedly worse, 2) moderately worse, 3) minimally worse, 4) no change, 5) minimally improved, 6) moderately improved, 7) markedly improved. However, patients may not recall accurately how they felt at baseline or be uncertain about when baseline was supposed to be. Also, patients with severe symptoms who don't respond and patients whose symptoms were initially mild and have little room to improve may end up with similar change scores. Accordingly, symptoms were also assessed using an absolute scale. Change in dyspnoea can be calculated by subtracting scores. A 5-point Likert scale was used to document patients' current status: 1) not short of breath at all, 2) mildly short of breath, 3) moderately short of breath, 4) severely short of breath, 5) very severely short of breath.

Patients were placed at 45 degrees for all questioning. If patients were recently up and walking, at least 2 minutes of equilibration is required.

Change scores between responses at baseline and 6 hours on the 5-point Likert scale items and the VAS were calculated by subtracting the baseline value from the 6-hour value. These change scores were categorized as improvement, worsening and no change. Fisher's exact tests were used to compare the 3 groups by either definition on changes in the 5-point Likert scale

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

As 15 B-lines have been previously shown to be associated with worse outcomes, a difference of 15 B lines will be considered significant for this study.

10.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

Exploratory Endpoints	
Total DAOOH through 30 days post-discharge	Association of B-lines at discharge and 30 day outcomes
Time to reach B-lines $\leq$15	Association of baseline, discharge, and change of b-lines with 30 day outcomes
Change in physical exam findings	All Cause readmissions, All cause ED re-visits

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

If the distribution of 30 day 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.

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.

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

There is no planned formal interim analysis

10.5 SAMPLE SIZE OVERALL

This pilot study is powered to show a difference of at least 7 B-lines between treatment arms. With a total of 70 subjects (i.e. 35 in each arm), we will have 82% power to detect an effect size of 0.7 on the number of B-lines, where the type I error rate is controlled at 0.05 (two sided)..

Local Sample Size: As a multicenter study, the expected enrollment at IU is half the patients or 35. However, up to 50 patients may be enrolled depending on accrual rates at the other site.

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

If necessary and if appointed, 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.

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 PI 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.

Personal medical information may release or review the personal health data of study patients shall take place solely within circumstance, and 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 American Heart Association (AHA) and AHA's properly authorized representatives, the quality assurance unit, or 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 AHA.

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.

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 2 sites in the United States, with 3 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). Each site PI will be a member of the steering committee.

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

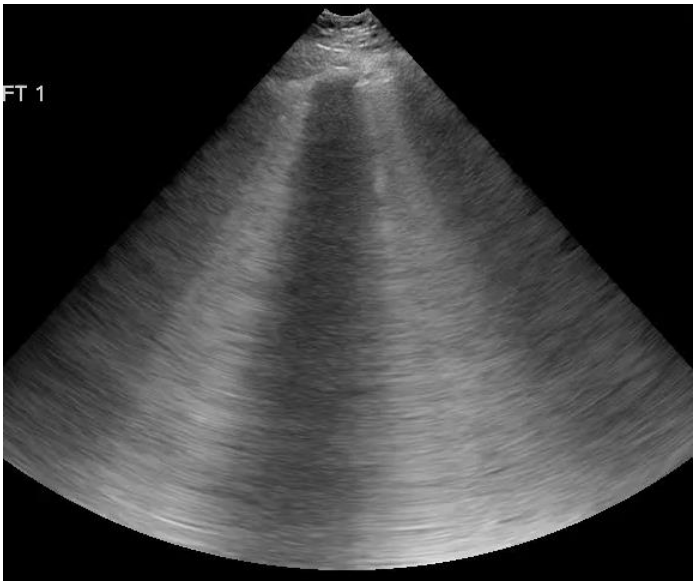
Each clinical site already has expertise in LUS (lung ultrasound). However, to minimize variation, a standardized teaching format will be utilized, emphasizing the 8 zone scoring system. Videos perform better to explain LUS and B-lines than a word document or PDF. Videos will be utilized for training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

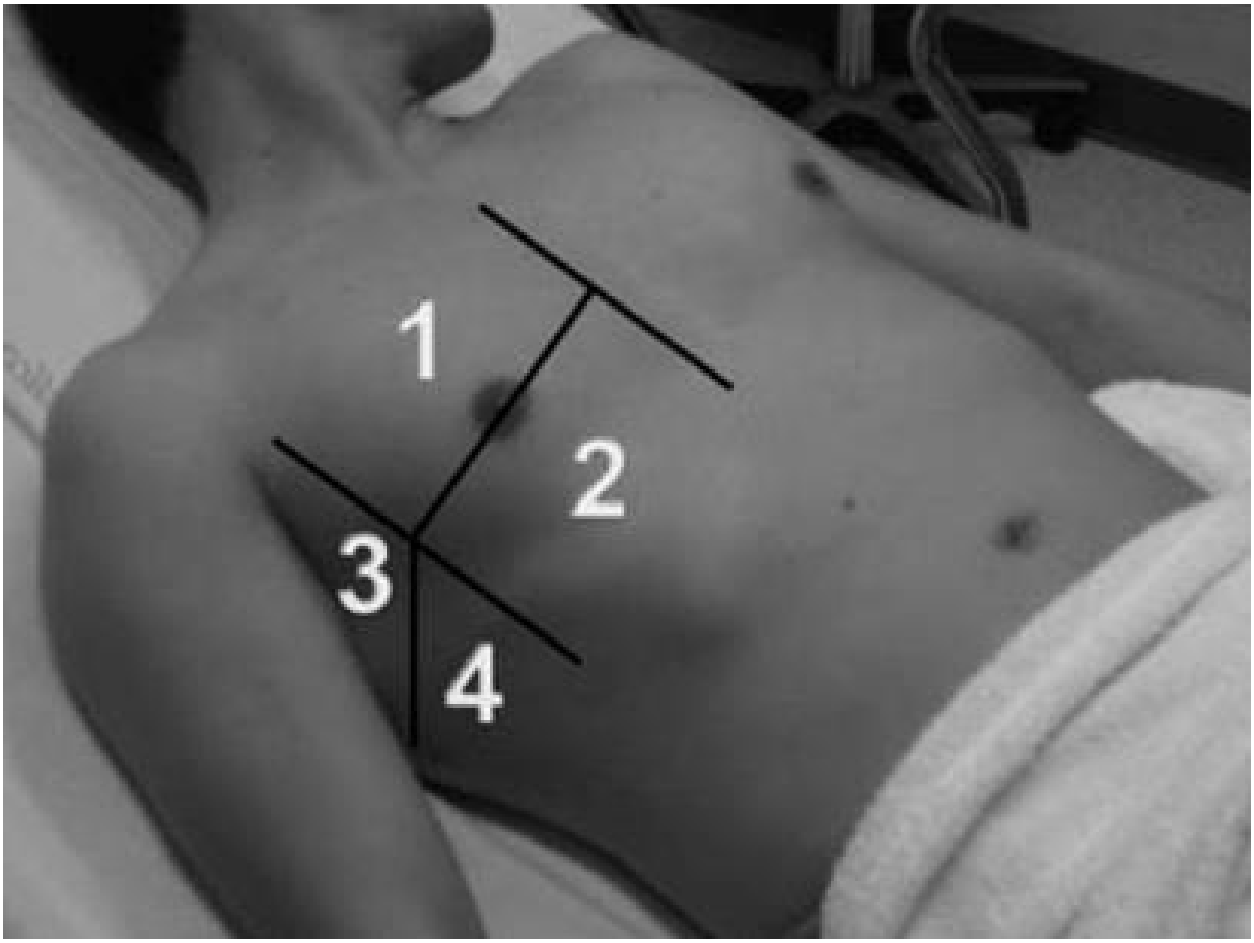


Lung (or pulmonary ultrasound) is one of the easiest ultrasound assessments to learn and perform. Even in patients with a high BMI, the lung can be evaluated. Additionally, lung ultrasound has high inter-rater agreement.

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

Below is the curvilinear probe used for the images.

Below is a pictorial representation of the 8-zone scoring system.



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

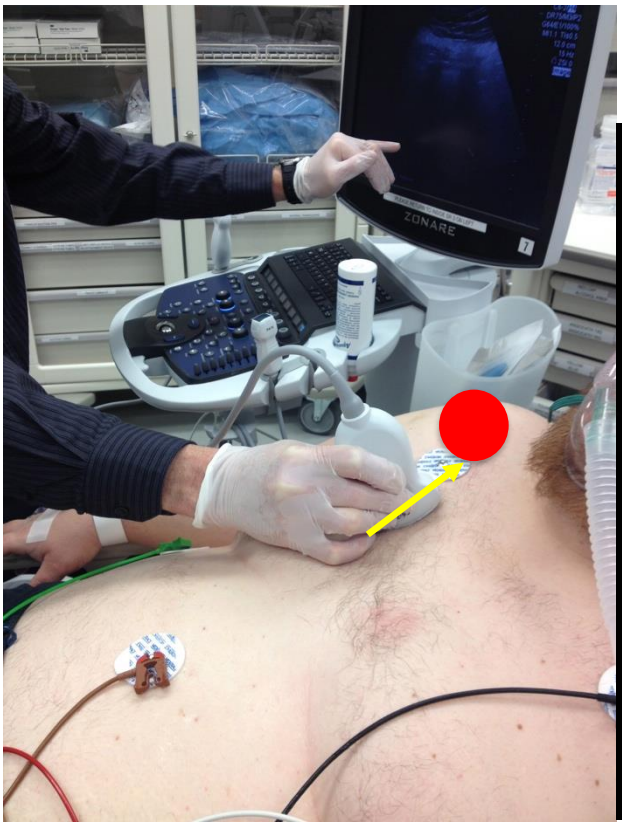
For scoring purposes, a B line cut off of 10 has been described previously in the literature. This allows for a more precise quantification of pulmonary edema. B lines will be counted as the number seen per acoustic window.

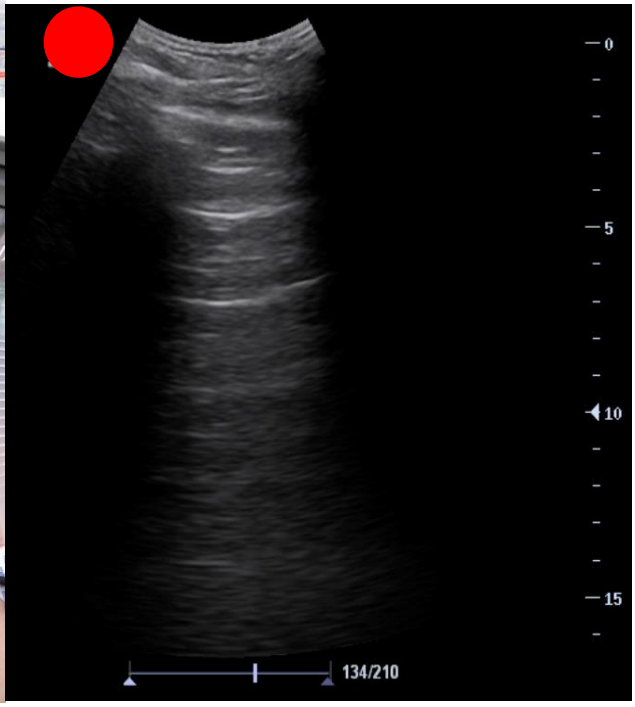
Machine settings

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

Image acquisition

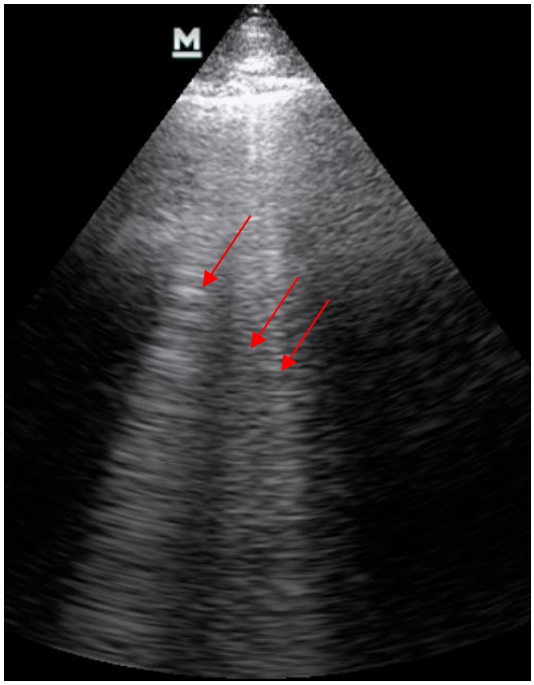
- Patient supine
- 45 degrees of bed elevation (as possible, if not possible please note on CRF)





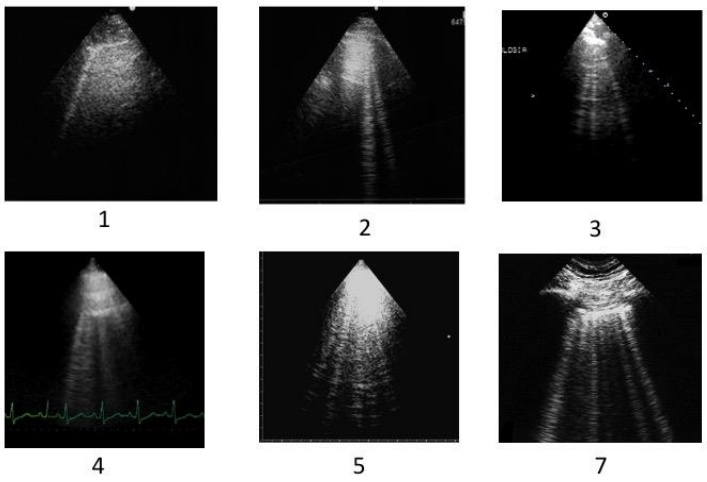
- Starting off on the **Right** in **Zone 1**: you want the indicator towards the patient's head. Identify ribs by shadowing and identify a rib space (see image below)
- Label R1
- Then turn 90 degrees with **indicator towards patient's right** so you are still in a rib space but the probe is **HORIZONTAL**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

COUNTING B LINES

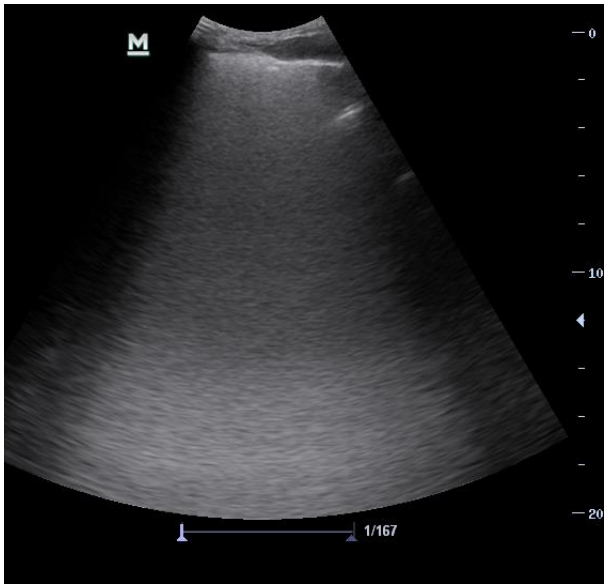


- B lines are vertical echogenic artifacts that originate from the pleural line and extend to the bottom of the ultrasound screen
- Below image is an example of how to count individual B lines

Figure 3: Counting of B-lines using Lung Ultrasound



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



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

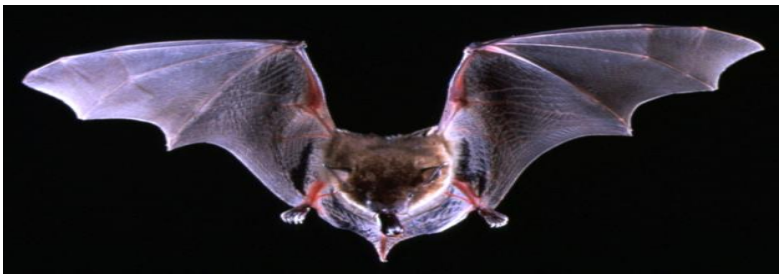
For lung ultrasound we rely on the imaging of artifacts to interpret our scans. The main artifact in the lung we see is called reverberation artifact. The physics behind this artifact is briefly explained below.

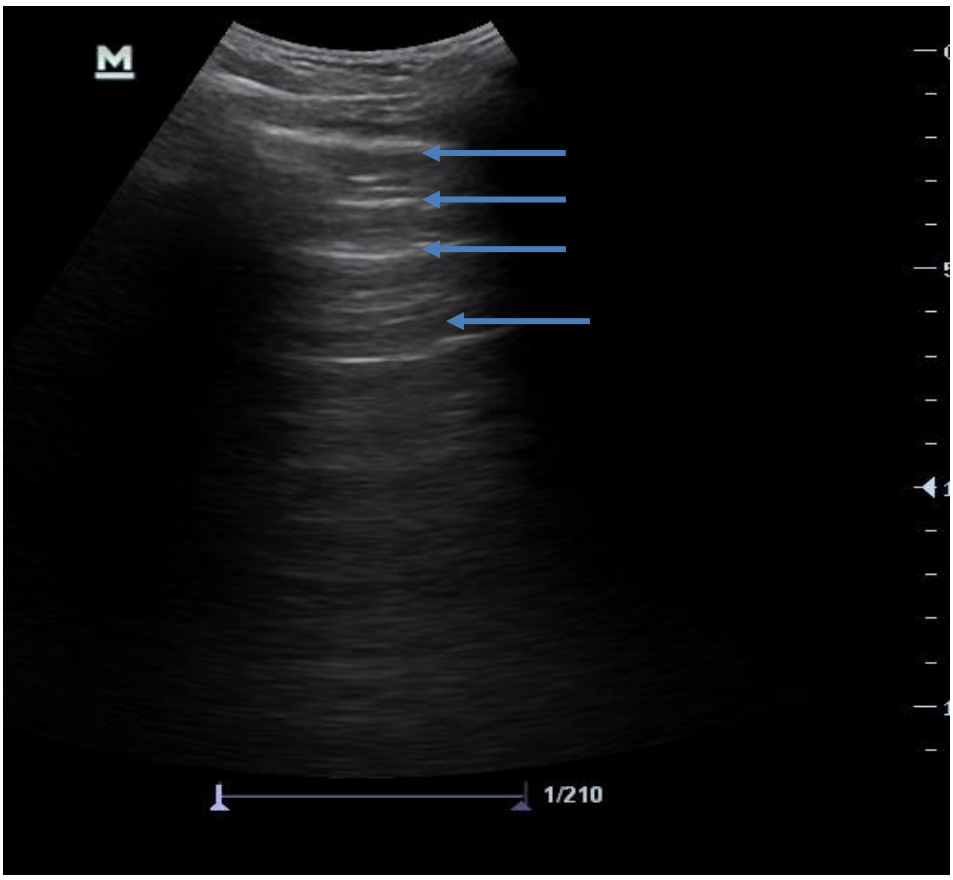
The ultrasound probe is constantly sending ultrasound waves towards whatever tissue is being imaged. When these sound waves get caught between 2 parallel surfaces that are highly reflective, they can bounce around between these highly reflective surfaces and take longer to return to the ultrasound machine.

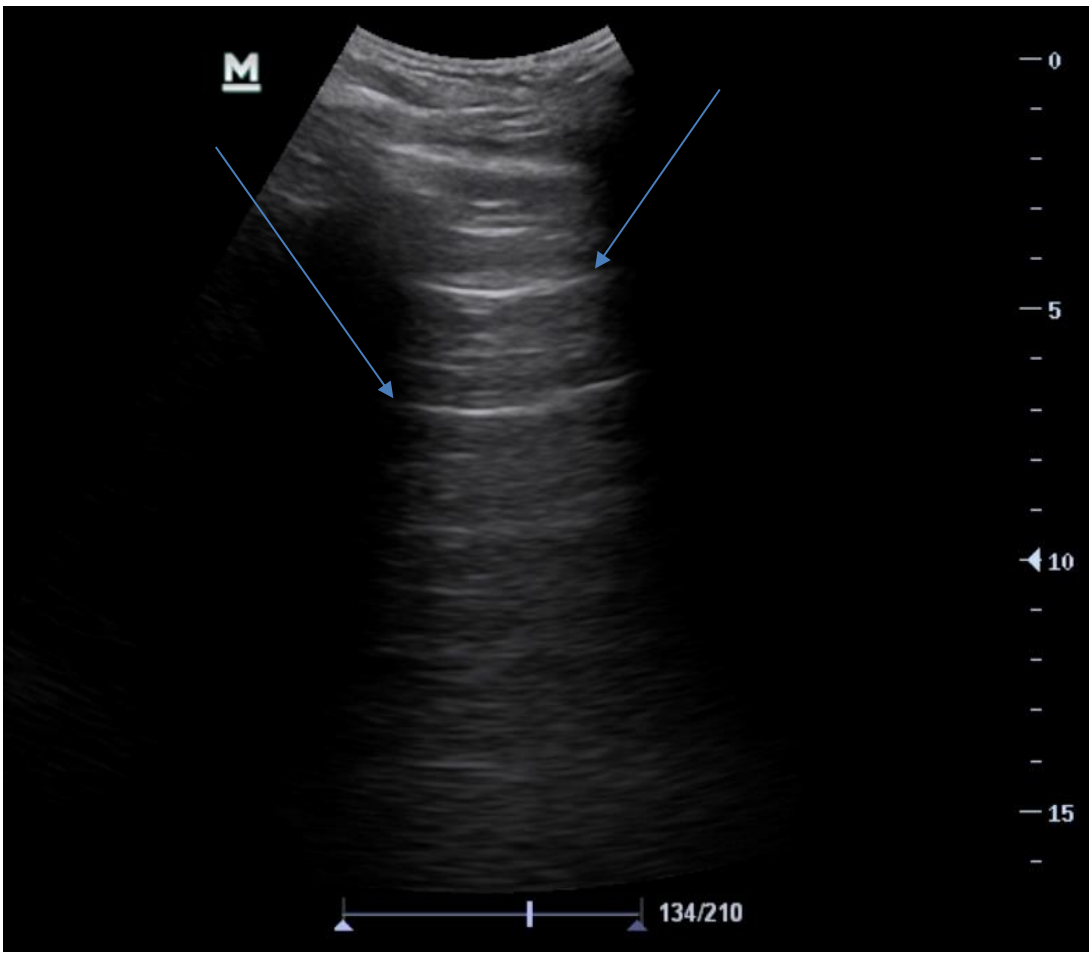
When this happens, you can have an echo that returns to the transducer after a single reflection and this echo will be displayed on the machine in the proper location. Sequential echoes may take longer to return to the transducer, and due to this increase in time the machine thinks that it is from a 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.

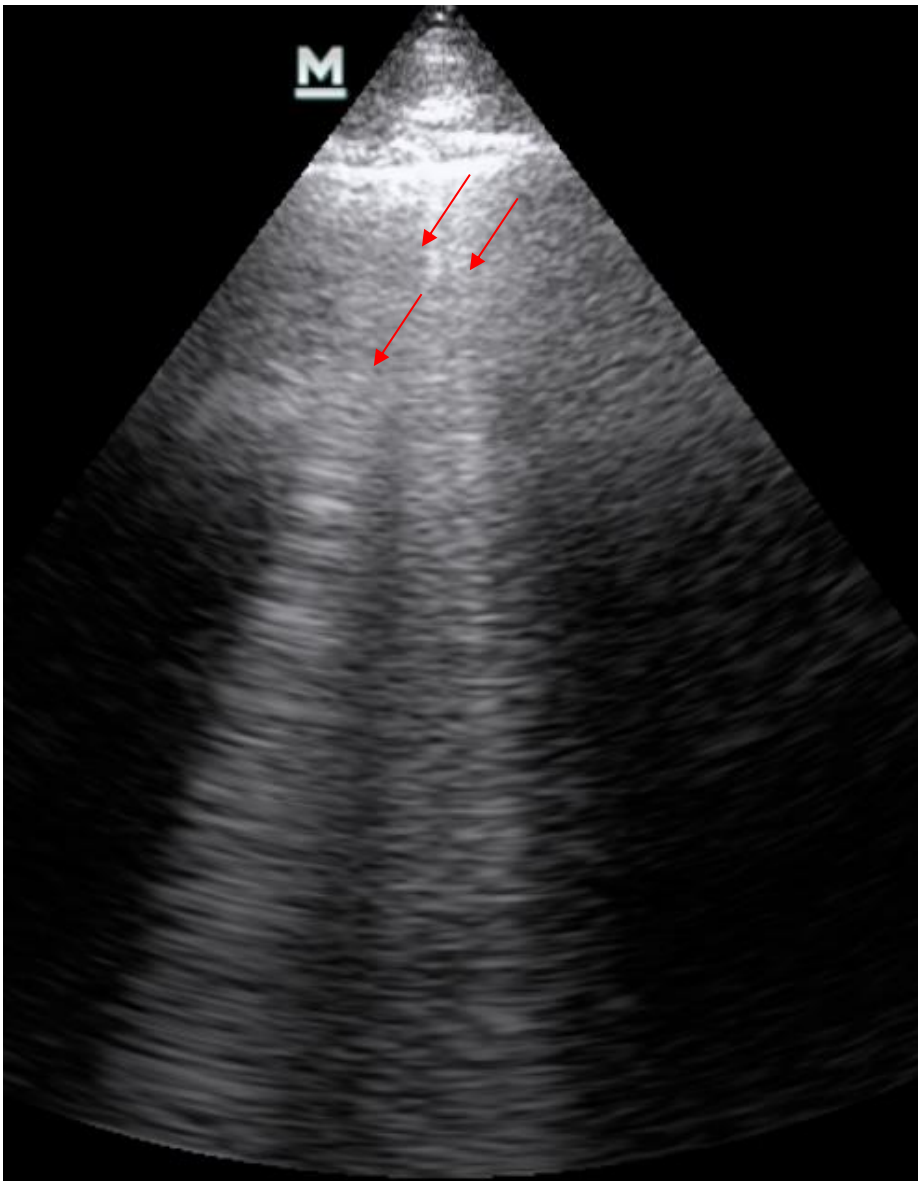



M
1/210


M
0
5
10
15
134/210

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.

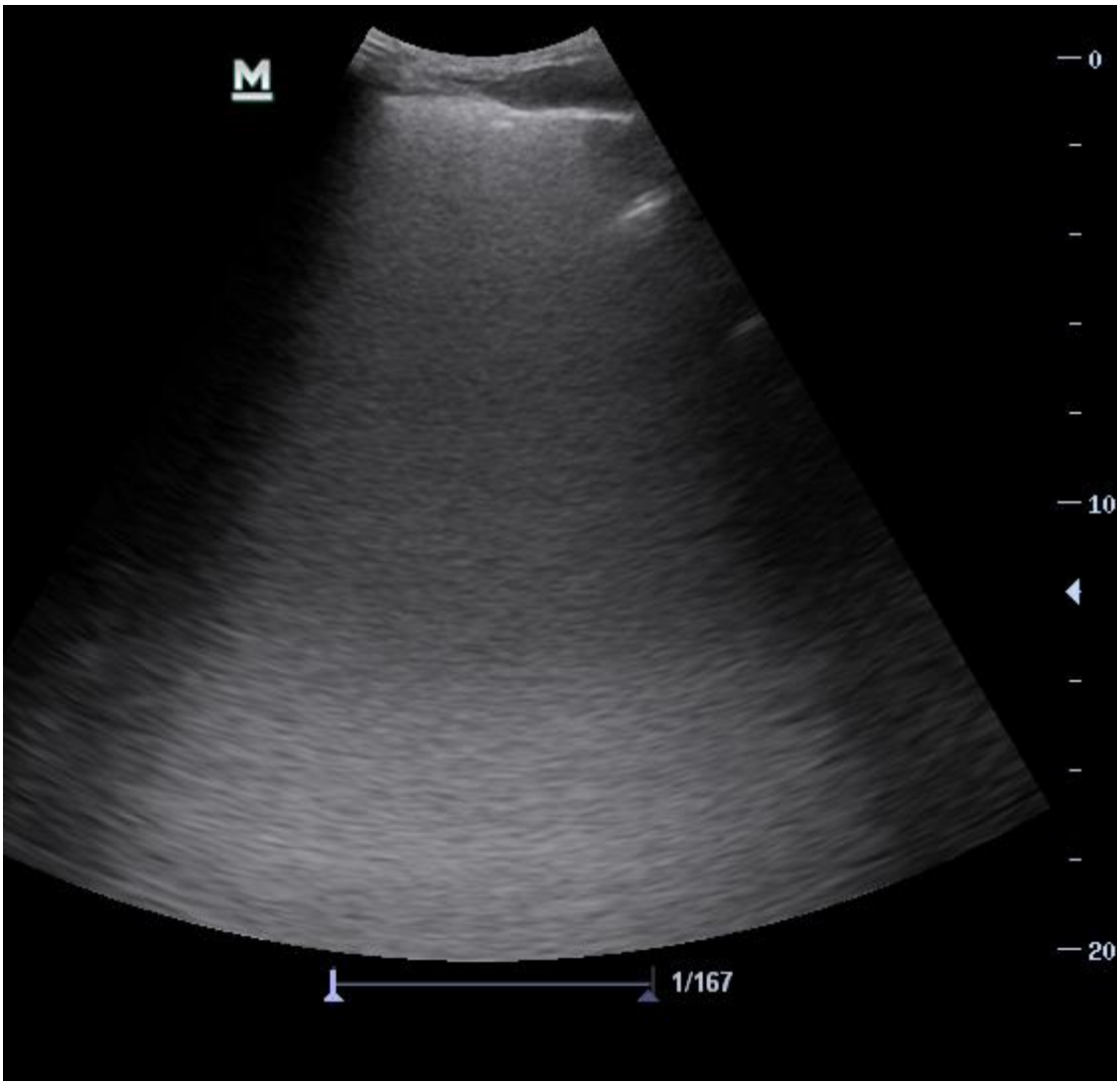
Normal patients have < 3 B lines per rib space



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

Under the strict supervision of Indiana University data stewards, we will utilize IU BOX HEALTH, an online cloud storage and collaborative environment. IU BOX HEALTH 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

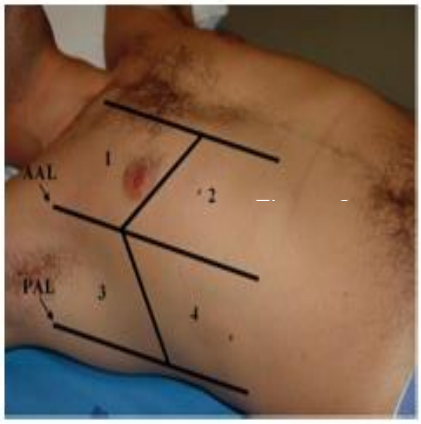
The correlation between B-lines on lung ultrasound and AHF has been well-established. B-lines are an assessment of extra vascular lung water (EVLW). Past studies demonstrate correlation of B-line artifacts with the following: (1) natiuretic peptide levels, (2) invasive hemodynamics, (3) chest xray, (4) 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 hospitalization.

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)
    - T48: up to 48 hours after initial scan (Day 3) (+/- 12 hours)

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

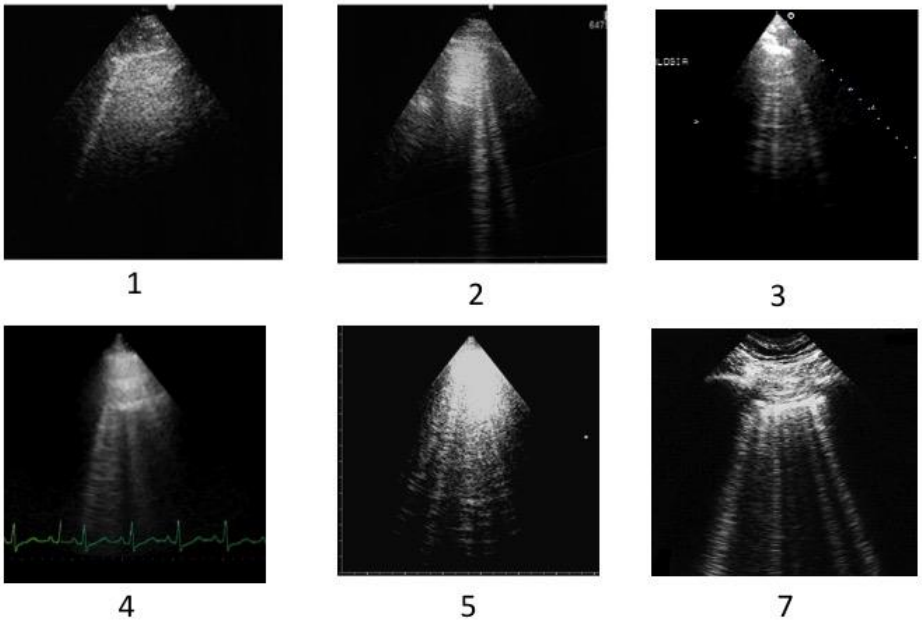
3) The gain settings will be standardized for all scans at each specific site. If equipment is the same, the gain will be standardized.

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 maxinum 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

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