Title: Effect of a Point-Of-Care Ultrasound-Driven vs Standard Diagnostic Pathway on 24-Hour Hospital Stay in Emergency Department Patients with Dyspnea

Acronym: POCUS PATHWAY

Trial Protocol

Version 2.2

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ClinicalTrials.gov number: TBD

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Contents

List of abbreviations

CE = conformité européenne

CRF = case report form

CONSORT = consolidated standards of reporting trials

CPR-number = civil registration number (danish: det centrale personregister)

CT = computed tomography

CXR = chest x-ray

ECG = electrocardiogram

ED = emergency department

POCUS = point-of-care ultrasound

SDP = standard diagnostic pathway

SPIRIT = standard protocol items: recommendations for interventional trials

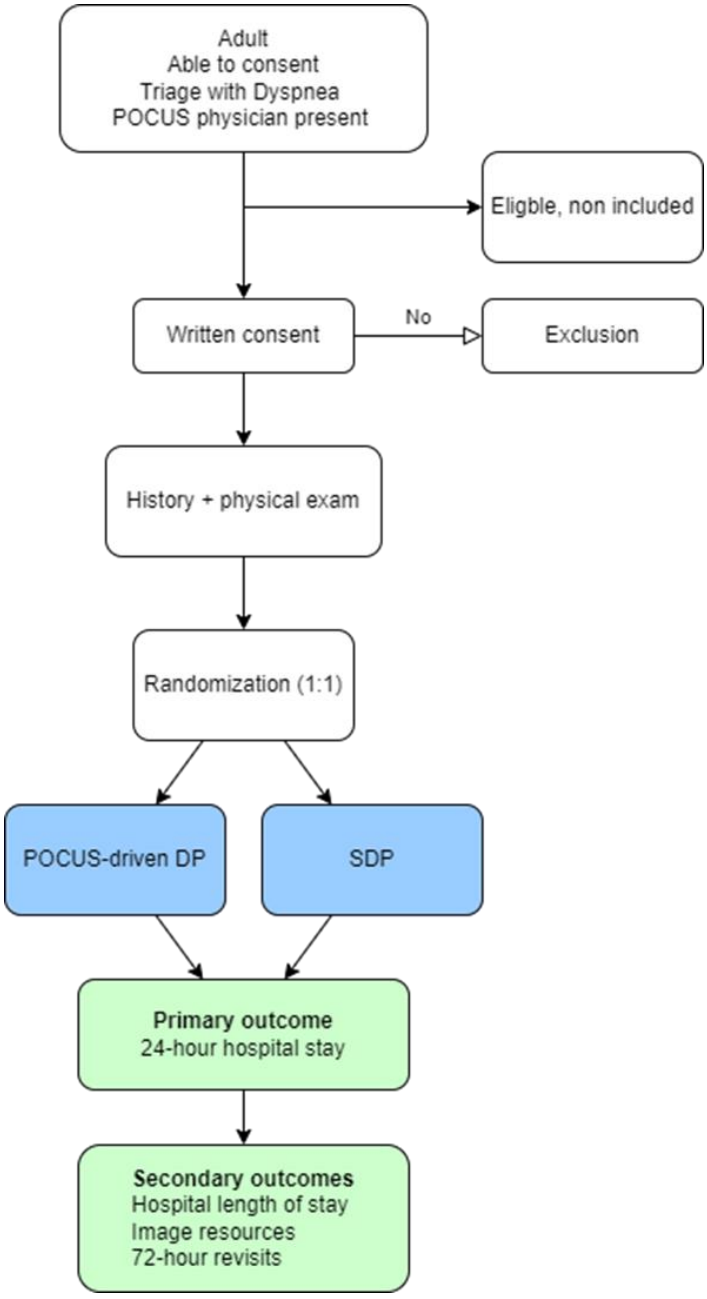
TBD = to be disclosed

95% CI = 95% confidence interval

Overview

Registry and trial number	TBD
Date of registration	TBD
Funding	"Puljen til styrkelse af sundhedsforskning i Region Midtjylland"
Primary sponsor	Stig Holm Ovesen
Contact	Stig Holm Ovesen, stigholm@clin.au.dk
Title	Effect of a Point-Of-Care Ultrasound-Driven vs Standard Diagnostic Pathway on 24-Hour Hospital Stay in Emergency Department Patients with Dyspnea
Country of recruitment	Denmark
Condition studied	Dyspnea
Intervention	1) Point-of-care ultrasound-driven diagnostic pathway
Comparator	2) Standard diagnostic pathway
Inclusion criteria	1) Emergency department contact 2) Age ≥ 18 years 3) Dyspnea as chief complaint 4) Including physician present
Exclusion criteria	1) Fulfilling of criteria for coded rapid-response teams (i.e., trauma, surgical or medical emergencies). 2) Prior enrollment in the trial 3) Prior focused lung or focused cardiac ultrasound in the current ED stay
Study type	Interventional Randomized (1:1) Intervention model: Parallel group Masking: Open-labelled
Date of first screening	January 4, 2023
Target sample size	642
Recruitment status	Not started
Primary outcomes	24-hour hospital stay
Key secondary outcomes	(1) hospital length of stay (2) image resources (3) 72-hour revisits

Trial flow



SDP = standard diagnostic pathway

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Revision chronology

Version 2.1, 221031

- **7.1 Data collection, management, and storage**
    - Clarified that data from medical records are passed on from the hospitals to the project.
    - Elaboration on the collection and type of data in the screening-log including patient data from patients that have not consented.
    - Specifying the obligation to GDPR and Danish data protection law
- **13. Funding and economy**
    - Specifying that results will be sought published no matter negative, positive, or inconclusive.
    - Elaborating on potential conflicts of interest and economic connections between funds and stakeholders and the primary investigator.
- **15. Data sharing**
  Clarifying that the data sharing policy described could result in the sharing of completely anonymized data to foreign countries.

1. Introduction

Acute dyspnea is a dominating chief complaint in emergency departments (ED) worldwide.[1-6] Triage systems that take patients chief complaint into consideration include either "Dyspnea" or equal synonyms (i.e., "Shortness of breath" or "Breathlessness").[4,7-10] Nevertheless, diagnostic uncertainty is still substantial due to unspecific and overlapping symptom complexes in disorders causing dyspnea, most frequently: chronic obstructive pulmonary disease, pneumonia, heart failure, pulmonary embolism, and asthma.[11-15] The evaluation of dyspnea is highly dependent on medical history and physical examination. But despite the additional usage of electrocardiograms, chest x-rays, arterial blood gas analysis, and large venous blood sample test panels, expert adjudicators post discharge still identify 30–40% of dyspneic patients with incorrect presumptive ED diagnoses.[16-19]

Point-of-care ultrasound (POCUS) poses as a potential valuable test in the diagnostic work-up of ED patients with acute dyspnea. The clinical performance of focused lung and cardiac ultrasound is well-founded to equalize or outperform other isolated diagnostic tests currently used for the spectrum of disorders causing acute dyspnea , but the clinical benefit is still unclear.[20-27]

To our knowledge no studies have found evidence that a diagnostic pathway guided by POCUS results in better patient outcomes. However, recent studies have found promising results for a simplification of the healthcare process, i.e., shorter hospital admission.[19,28,29] In emergency departments, Riishede et al. examined the accuracy of POCUS added onto the existing diagnostic pathway but secondarily found an increased rate of 24-hour hospital stays in favor of the POCUS-group.[19] In cardiopulmonary patients admitted to an internal medicine department, Cid et al. investigated the effect of POCUS added onto the diagnostic pathway at this timepoint in the hospital stay. In favor of the POCUS-group, they found a difference in length-of-stay of 11.9 hours, which was not significantly different. Notably, the second half of the cohort (according to the inclusion period) seemed to be driving all of the potential effect, indicating that a long lead-in period in this study could have increased the vulnerability to underestimating the true effect. Both Riishede et al. and Cid. et al. applied POCUS as an add-on to the standard diagnostic pathway and had sonographers other than the treating physicians to perform the POCUS examination.

We regard one of the greatest potentials of POCUS to be the augmented diagnostic certainty that it can give treating physicians during the initial history and physical examinations, thereby helping them to construct the most appropriate diagnostic pathway for each individual patient. Bearing this in mind, a

simplification of the healthcare process would be most likely under an implementation where confident treating ED physicians apply POCUS themselves and integrate their findings into clinical practice, letting it guide the remaining diagnostic pathway. Given the signalling trends that remained in Riishede et al. and Cid et al. despite potential shortages, we hypothesize that such a POCUS intervention would potentially lead to a more efficient healthcare process.

To further understand whether a point-of-care ultrasound-driven diagnostic pathway compared to a usual diagnostic pathway improves and simplifies healthcare processes for emergency department patients with dyspnea, we designed this trail.

2. Objectives and hypothesis

The primary aim of the study is to determine the effect of a point-of-care ultrasound-driven diagnostic pathway in dyspneic ED patients on 24-hour hospital stay when compared to standard diagnostic pathway.

The secondary aims are to investigate the effect of a point-of-care ultrasound-driven diagnostic pathway on: (1) hospital length of stay; (2) image resources; (3) 72-hour revisits; (4) 30-day hospital free days; (5) time to treatment.

Two sub-studies are planned a priori. One is investigating the diagnostic thinking efficacy (Frybach and Thornbury Level 3 [30]) by exploring the effect of POCUS on the following measures: (1) number of differential diagnoses; (2) diagnostic pre- and post-test probabilities; (3) experienced benefit of testing from the physicians' perspective; (4) patients' experiences; (5) concurrent treatment; (6) change in diagnosis from ED contact to hospital discharge. The other is exploring the effect of POCUS on measures and scores for clinical deterioration (i.e., early warning and organ failure scores).

3. Trial design

3.1 Overview

This trial is designed as a multi-center, randomized, investigator-initiated, open labelled, pragmatic, controlled trial with two parallel groups.

3.2 Randomization

Patients will be randomized in a 1:1 ratio to either a point-of-care ultrasound-driven diagnostic pathway or SDP in permuted blocks with random sizes of 2, 4, or 6, stratified to site. Unique randomization numbers (Study ID) for each patient will be generated according to each site and stratification variable. The randomized sequence of Study IDs will be generated using online randomization software. Randomization envelopes will be prepared and packed by a company independent of the trial based on the randomization sequence. The company will send the packed randomization envelopes to the coordinating investigator. For 1% of the produced envelopes selected by a random number generator, the coordinating investigator will open these envelopes to check that the inside texts match the provided allocations. The remaining envelopes will then be stored centrally in a safe and locked location – from here, they will be shipped to participating stations based on their current tally and inclusion rate. Finally, the randomization sequence will be printed and signed by two independent individuals, stored in a sealed opaque envelope in the trial

master file, and only concealed until after completion of all trial-related procedures and statistical analyses are finalized.

3.3 Interventions

3.3.1 Point-of-care ultrasound-driven diagnostic pathway (Intervention)

The intervention is focused lung and cardiac ultrasound performed as an extension to physical examinations plus diagnostic decision recommendations based on those test results (a point-of-care ultrasound-driven diagnostic pathway). Per protocol diagnostic decision recommendations will be provided for the treating physician, but only for specific ultrasound findings. Final decision on next-line imaging and further diagnostic testing should incorporate history and other physical examinations and will remain upon the treating physicians' discretion.

Point-of-care ultrasound will be performed by the treating ED physician at the discretion of her timing and workflow, as well as preference of ultrasound apparatus, transducer, and pre-set. The assessment will include focused lung and focused cardiac ultrasound; in total, estimated to take approximately eight minutes [31]. Cine-loops are documented sequentially for all protocolized acoustic windows. Indeterminate or missed views that are not saved in cine-loops will be documented in a separate survey instrument. Findings and interpretation will be documented in the electronic patient record for clinical purposes.

Focused lung ultrasound will include 8 zones (anterior and lateral) and evaluate pneumothorax, interstitial syndrome, lung consolidation, and pleural effusion. Focused cardiac ultrasound will include four views (subxiphoid four-chamber view, parasternal long-axis view, parasternal short-axis view, and apical four-chamber view) and evaluate pericardial fluid, right ventricle dilation, and left ventricular systolic contractility.

Diagnostic decision recommendations will be developed based on existing literature, current guidelines, and steering committee consensus. They will be presented to including physicians in a suggested decision-tree including the most common etiologic causes of acute dyspnea. See supplementary material for a presentation of the diagnostic decision recommendations.

3.3.2 Standard diagnostic pathway (Control)

Standard diagnostic pathway will include, but not be limited to, blood samples, blood gases, electrocardiogram, and chest x-ray. Focused lung and cardiac ultrasound cannot be performed while the patients stay in the emergency department. Other POCUS modalities can be applied immediately (i.e.,

lower extremity compression ultrasound or focused abdominal ultrasound). Chest CT, CT angiogram, echocardiography, and other non-routinely performed tests remain exclusively upon the treating physicians' discretion.

3.3.3 Sonographer competence

Before including patients into the study, all sonographers will be assessed and graded in a lung and cardiac ultrasound simulation using objective competence instruments.[32,33] In addition, sonographers will fill a baseline instrument including information on their specialization and experience (clinical as well as ultrasound). Both the objective competence assessments and baseline information will be used in pre-defined sub-group analyses (see *section 6.2.5*.)

3.3.5 Ultrasound validation

An audit of ultrasound cine-loop quality will be performed post-hoc. In a random subgroup of ten percent of included patients weighted by the number of patients per physician and month of inclusion, audit will be performed in duplicate, on a 1-5 Likert-scale.[34,35] The scale is recommended by The American College of Emergency Physicians, [35] and this validity procedure has previously been applied in this research field.[34] The two auditors will be blinded for sonographer and patient characteristics, and they will be experienced users of point-of-care ultrasound as well as researchers in the field.

3.3.6 Diagnostic survey

The treating physician will complete a diagnostic survey twice: After the physician's primary assessment with/without POCUS, and after finalized initial SDP (blood samples, blood gas, ECG, and CXR). This will include a list of common cardiopulmonary conditions categorized. From this list the treating physician must select one primary diagnosis, an indeterminate number of differential diagnoses, and plot the diagnostic probability in the primary diagnosis on a visual analog scale from 0–100%. Lastly, the physician must grade the experienced benefit from different parts of the diagnostic work-up by using the following categories: "No new information", "New Pathology, but no further action needed ", "Further diagnostics needed", "Presumptive diagnosis changed", or "Immediate treatment needed".

3.3.6 Patients' experience questionnaire

Twenty-four hours after discharge, patients will receive an electronic questionnaire concerning their experiences from the emergency department stay. The questionnaire is adapted from the Danish Nation-Wide Patient's Experience Survey ("Landsdækkende Undersøgelse af Patientoplevelser"). Thereby, professional survey consultants have selected, formulated, and validated the questions. The questions

will be graded on a 1–5 Likert scale (from “Not at all” to “Very much”) with two alternative responses (“Don’t know” and “Not relevant for me”). See supplementary material for the content and layout of the survey.

3.4 Blinding

Blinding patients or clinical teams will not be feasible.

3.5 Trial procedures

3.5.1 Patients

The trial procedures will be limited to the point-of-care ultrasound-driven diagnostic pathway, the diagnostic survey, and the patient questionnaire; from there on, participation will only include data collection.

3.5.2 Clinical personnel

Prior to the beginning of patient enrollment and continuously throughout the enrollment period, the clinical teams involved in the treatment of dyspneic patients at the participating hospitals will be informed about the trial. Clinical personnel will be informed about the background and objectives of the trial, the inclusion/exclusion criteria, the interventions, and the trial procedures they are involved in. We anticipate formal, in-person didactics continuously, with informal sessions and emails as applicable in between, as well as an educational video.

4. Setting and Patient population

4.1 Setting

Physicians and patients from multiple emergency departments will be included, university hospitals as well as regional hospitals and Danish as well as international sites are welcomed. The following Danish emergency departments are expected to include patients: Horsens, Goedstrup, Aarhus, Randers, Odense, and Slagelse. An updated list of study sites can be obtained from the trial website when inclusion is ongoing (TBD).

4.2 Inclusion criteria

1) Emergency department contact
2) Age ≥ 18 years
3) Triaged with Dyspnea (or similar, i.e., Breathlessness) as chief complaint in the local triage system

4) Including physician present

4.3 Exclusion criteria

1) Fulfilling of criteria for coded rapid-response teams (i.e., trauma, surgical or medical emergencies).
2) Prior focused lung or focused cardiac ultrasound in the current ED stay
3) Prior enrollment in the trial
4) Unable to consent
5) Non Danish-speaking

4.4. Double inclusion

Inclusion in this study will restrict patients from inclusion in other studies.

4.5 Site inclusion

Study centers will be included on the basis of emergency department physicians who wish to participate. Participating physicians must have: 1) certified competence in point-of-care ultrasound; 2) an experience of >50 cardiac and lung scans; 3) clinical experience corresponding to three post-graduate years; 4) be in residency training or be specialized; and 5) be working in emergency medicine.

5. Outcomes

5.1 Primary outcome

The primary outcome, 24-hour hospital stay, will be defined as the proportion of patients having a hospital stay (from ED arrival to hospital discharge) of less than 24 hours.

5.2 Secondary outcomes

Hospital length-of-stay, defined from ED arrival to hospital discharge, will secondarily be analyzed non-binarily.

Image resources will be quantified in numbers of the following imaging techniques performed during the current hospital stay: chest x-rays, echocardiography, computed tomography (CT) angiography, and CT thorax.

72-hour revisits will be defined as a composite outcome including any unplanned hospital stay within 72 hours from the previous hospital discharge, in-hospital mortality, and mortality within 72 hours from the previous hospital discharge.

Hospital-free days will be defined as the number of days within the 30-day period following hospital discharge where the patient is not hospitalized and alive.[36] In-hospital death will be computed as zero hospital-free days. Registrations showing that a patient has left home for a hospital errand will be computed as one day that was not hospital-free (i.e., outpatient or paraclinical follow-up visits). Long- or short-stay nursing facilities, inpatient hospice facilities, or rehabilitation facilities will count as hospital-free, as will all days at home, including those with home-based medical services.[36] For technical reasons we will divide the number of hospital-free days by 30 to produce an outcome in the range 0 to 1 where high is good.

Time to treatment will be defined as time from ED arrival until administration of any of the following predefined subgroups of treatment: antibiotics, diuretics, anticoagulants, bronchodilators, and systemic steroids. Only ED administrations will be included. Oral and intra-venous treatments will not be separated. 5.3 Sub-study outcomes

From the diagnostic survey, "Number of differential diagnoses" will be computed as the sum of selected diagnoses in the survey.[37,38] "Diagnostic pre- and post-test probabilities" will be defined as the percentage of diagnostic probability for the primary diagnosis filled in repeated surveys.

The experienced benefit of testing from the physicians' perspective will be defined at baseline for the objective examination with or without POCUS, compared to the patient history. Later, after finalized initial SDP, gradings for each of: blood analyzes, blood gas, ECG, and CXR will be defined and compared with the baseline benefit from history plus objective examination with or without POCUS.

Patients' experiences will be defined on the ordinal scale described in *Section 3.3.6*.

Concurrent treatment will be defined as either of the following drug-combinations: corticosteroids plus intravenous diuretics or antibiotics plus intravenous diuretics, administered within the first two hospital days.[39]

Change in diagnosis from ED contact to hospital discharge will be defined as a difference between the ED primary diagnosis (from the second diagnostic survey) and the hospital discharge diagnosis categorized as previously described.[15]

Clinical deterioration will be defined as a composite outcome of multi-organ failure, intensive care unit admission or death within 72 hours from ED admission. Multi-organ failure will be defined as a rise in Sequential Organ Failure Assessment (SOFA) score of at least two.[40] Additional outcomes exploring other scores and measures for clinical deterioration will be added in a future amendment to the protocol.

5.4 Harms

Point-of-ultrasound is considered safe and commonly used in clinical practice. The overall benefit and potential harm of the interventions will be captured in our primary and secondary outcomes. See the ethical section (*9.1*) for considerations of potential harm.

6. Sample size calculation and Statistical analysis plan

6.1 Sample size calculation

Based on a previous study with a similar population, the proportion of patients discharged within 24 hours is expected to be 24%.[19] This proportion is in accordance with similar summarized proportions computed from business intelligence data from emergency departments in Central Denmark Region for the last two months and last two years. Riishede et al. found that 40% of patients in the POCUS-group were discharged within 24 hours, corresponding to a risk difference of 16% (24% versus 40%). We regard a risk difference of 10% clinically relevant and want to apply conservative expectations. This will secure power in case the effect is not as pronounced as found by Riishede et al. Based on a chi-squared test and an alpha of 0.05, a sample size of 642 patients (321 per group) is needed to obtain 80% power.

6.2 Statistical analysis plan

6.2.1 General considerations

The statistical analyses and reporting of the primary manuscript will adhere to the Consolidated Standards of Reporting Trials (CONSORT)-guidelines. All tests will be two-sided, a p-value <0.05 will be considered significant, and all confidence intervals will have 95% coverage. Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram (see supplementary material for a draft).

All analyses will be conducted on a strict intention-to-treat basis including patients by their group allocation if they meet all inclusion criteria and no known exclusion criteria at the time of POCUS.

The two groups will be compared in relation to baseline characteristics using descriptive statistics. The persons conducting the statistical analysis will be blinded to the randomization and groups will be

designated as "A" and "B" until all pre-specified analyses are performed, two conclusions have been written, and have been agreed between all authors.

6.2.3 Analysis plan overview

Outcome	Measure	Estimate
24-HOUR HOSPITAL STAY (PRIMARY)	Number (Proportions)	Risk difference and relative risk
Hospital length-of-stay	Incidence	Hazard ratio and Sub-distribution hazard ratio
Image resources	Number (Proportions)	Risk difference and relative risk
72-hour revisits	Number (Proportions)	Risk difference and relative risk
30-day hospital-free days	Mean	Mean difference
Time to treatment	Incidence	Hazard ratio

6.2.4 Primary outcome

The primary outcome will be presented as the absolute number and incidence proportions in each group. Groups will be compared using risk difference and relative risk with 95% confidence intervals and a p-value will be calculated based on a likelihood ratio test.

6.2.5 Secondary outcomes

Hospital length-of-stay will be analyzed using time-to-event analysis. Both hazard and cumulative incidences will be analyzed and reported side-by-side. The Aalen-Johansen estimator will be applied to estimate the cumulative incidence in the intervention and control group. The Fine-Gray model will be used to compute the sub-distribution hazard ratio, considering the competitive risk of in-hospital death. Cox regression will be used to compute the cause-specific hazards and the overall hazard.[41]

Image resources will be presented as a composite absolute number and incidence proportion counting the cumulative number of participants having received any of the diagnostic tests mentioned in *Section 5.2*. Comparison between groups will be performed using risk difference and relative risk with 95% confidence intervals and a p-value will be calculated based on a likelihood ratio test. The absolute numbers and incidence proportions of each diagnostic test will be reported descriptively ordered by group.

72-hour revisits will be presented as the composite outcome with cumulative number of events and incidence proportions with 95% confidence intervals. Comparison between groups will be presented as risk difference and relative risk with 95% confidence intervals and a p-value will be calculated based on a

likelihood ratio test. The absolute numbers and incidence proportions of patients admitted within 72 hours, dying in-hospital, and dying within 72 hours will be reported descriptively ordered by group.

30-day hospital free days will be presented as raw means in the two groups with 95% confidence intervals. Comparison of the intervention-effect will be quantified in a mean difference from the likelihood function underpinning the likelihood ratio test described below. To produce a p-value, a likelihood ratio test will be built upon a logistic model for mortality and a linear regression for days alive outside hospital within 30 days for patients who are discharged alive within 30 days (a tobit regression model).

Time to treatment will be presented as a composite outcome with a median and interquartile interval for both groups. Comparison will be performed by using cox regressions analysis with study time as time scale. Treatments are commonly administered within the first 1–6 hours and before the competing events as death, intensive care or other inpatient unit admission. Therefore, they will all be censored. A hazard ratio with 95% confidence interval and a p-value will be presented.

6.2.6 Subgroup analyses (primary manuscript)

Subgroup analyses will be performed on the relative scale for the primary outcome. The trial is not powered to detect subgroup differences, and these will be considered exploratory and hypothesis generating. Subgroup analyses will be performed according to: (1) ED arrival (day, evening, or night); (2) weekdays or weekend/holiday; (3) physicians' ultrasound objective competence categorized; (4) physicians' post-graduate years categorized; (5) prehospital presumptive diagnosis; and (6) 10-year patient-age intervals.

6.2.7 Sensitivity analyses (primary manuscript)

Four pre-planned sensitivity analyses will be performed to investigate the influence of "sonographer-variation" and "physician investigator effect" on the primary outcome.

To examine the hierarchical influence from "sonographer-variation" on the primary outcome, relative differences with 95% confidence intervals will be obtained from a logistic regression model with the stratification variable "treating physician" included as a random effect.

To examine the influence from "physician investigator effect" on the primary outcome, the primary analysis plan described in *Section 6.2.3* will be repeated stratified by two physician investigator related variables: "discharging physician" (physician investigator or another physician) and "physician investigator responsible time" (the physician investigator was the responsible physician assigned to the included patient in more than the first eight hours of ED stay, yes/no).

To examine the effect of the different diagnostic roles of ultrasound on the primary outcome, the primary analysis plan will be repeated in an as-treated analysis. Patients will be grouped into a POCUS-add-on group and a POCUS-replacement group which are the two diagnostic pathway scenarios from the point-of-care ultrasound-driven diagnostic pathway.

6.2.8 Missing data

Missing data will be reported for all relevant outcomes and characteristics. We do not expect any missing data for the primary or secondary outcomes.

6.2.9 Sub-study outcomes

Number of differential diagnoses will be presented as median with interquartile interval (25th and 75th percentiles) in each group. Comparison between groups will be performed by using ordinal regression modelling for the total number of differential diagnoses in the second survey as well as for the delta number of diagnoses between the two surveys. Additionally, exploratory binary risk estimates will be computed and compared using likelihood ratio tests for the following outcomes: proportion of patients with less than three differential diagnoses in the second survey and proportion of patients with a reduced number of differential diagnoses.

Diagnostic pre- and post-test probabilities will be presented as means with standard deviation in each group. Comparison will be performed by using the student's t-test for the mean from the second survey as well as for the mean-difference between the paired surveys. The proportion of patients with an unchanged diagnostic probability (difference below ten percentage-points) will be computed and compared with risk estimates and a likelihood ratio test.

Sub-group analyzes will be performed exploratory for all abovementioned outcomes for number of differential diagnoses and diagnostic probabilities, according to the following variables: (1) change in diagnosis between ED contact to hospital discharge; (2) physician ultrasound competence; (3) prehospital presumptive diagnosis.

Physicians' experienced benefit of testing will be dichotomized for comparison analysis and presented with risk estimates and 95% confidence intervals and a p-value from a likelihood ratio test. For descriptive comparison, category-distributions will be figured by group.

Patients' experiences will be treated continuously, comparing mean scores between groups using a unpaired t-test. For descriptive comparison, category-distributions will be depicted by group.

Concurrent treatment will be presented as a composite absolute number and incidence proportion counting the cumulative number of participants having received any of the concurrent treatment combinations. Comparison between groups will be performed using risk difference and relative risk with 95% confidence intervals and a p-value will be calculated based on a likelihood ratio test. The absolute numbers and incidence proportions of each treatment combination will be reported descriptively ordered by group.

Change in diagnosis from ED contact to hospital discharge will be presented as the absolute number and incidence proportions in each group. Groups will be compared using risk difference and relative risk with 95% confidence intervals and a p-value will be calculated based on a likelihood ratio test.

The analysis plan for the clinical deterioration outcomes, for the second sub-study, will be added in a future protocol amendment.

7. Data collection and management

7.1 Data collection, management, and storage

Sonographer characteristics and objective competence, case report form (CRF), diagnostic surveys, and patient questionnaires will be collected prospectively in a REDCap® database. Only limited data will be obtained in the CRF (see *section 7.2.1*). The CRF will be available in a paper and electronic format. The paper-CRF will be filled during all prospective screenings and stored securely, according to legal regulations. Site investigators will monitor and enter the paper-CRF data from non-included patients into the electronic database. The electronic-CRF (eCRF) will be filled by the treating physicians in included patients.

Few, completely anonymized patient characteristics will be passed on from the hospital to the project before consent, in all screened patients. This screening log data will be passed on from the hospitals' business intelligence data warehouses encompassing routinely collected data from the electronic medical record. The screening log will for all screened patients include the following variables: age, gender, hospital length-of-stay, and the number of patients fulfilling inclusion criteria and exclusion criteria. Screening log data will be used in the study to describe patient flow in the CONSORT diagram (see variables in overview 7.2.1).

Consent forms will be stored securely, according to legal regulations. Site investigators will monitor their storage and enter available data into the electronic database (i.e., treating physician name, patient name and contact information).

To minimize missing data, SMS-reminders with direct data-entry links to the diagnostic survey in REDCap® will be sent to treating physicians at four hours post randomization.

Baseline characteristics, vital parameters, biochemical and microbiologic results, treatments, admission metrics (timing and units), readmissions, and mortality will be collected retrospectively by using routinely collected patient-record data passed on from regional data warehouses.

The primary assessment findings, ultrasound findings, and radiologic findings will be manually entered into a REDCap® database based on independent, duplicate review of the medical records.

All data will be collected longitudinally using the personal identification number as key identifier.

Every physician including patients will have access to data capture instruments in REDCap®. Members of the steering committee will have access to the entire database and user management. All data entries in REDCap® will use the same linkage between a record ID and personal identification number.

All routinely collected, data warehouse, data have 100% completeness of identifiers and are linked by using entity keys for the personal identification number. Routinely collected data will be linked to REDCap-data by using the personal identification number.

All data will be kept in a secure content management system (Hyland Alfresco™, Boston, Massachusetts, USA). Data management will be computed by using STATA® (Statacorp, Houston, TX, USA).

Ultrasound film clips will be stored securely, according to local legal regulations.

Data handling will comply with General Data Protection Regulation (European Union 2016/679) and the Danish act for data protection (ACT 502 of 23rd May 2018).

7.2 Variables

7.2.1 Overview

A detailed data dictionary that clearly defines all included variables will be created prior to patient enrollment. The data dictionary will provide the name of the variable (including the code used in the database), a detailed definition of the variable, categories for categorical variables, and units and ranges

for continuous variables. Below is provided a brief overview of the included variables but details are reserved for the data dictionary. The following variables will be obtained on all included patients:

Variable	Collection	Source	Purpose
Before consent, all screened patients			
Site	Retrospective	Paper-CRF or BI data *	Screening log
Treating physician	Prospective	Consent form	Screening log
INCLUSION CRITERIA			
Emergency department contact	Retrospective	Paper-CRF or BI data	Screening log
Age ≥ 18 years	Retrospective	Paper-CRF or BI data	Screening log
Triaged with Dyspnea as chief complaint	Retrospective	Paper-CRF or BI data	Screening log
Including physician present	Prospective	Duty schedule	Screening log
EXCLUSION CRITERIA			
Coded rapid-response teams	Retrospective	Paper-CRF or BI data	Screening log
Prior focused lung or focused cardiac ultrasound in the current ED stay	Prospective	Paper-CRF	Screening log
Prior enrollment in the trial	Retrospective	Paper-CRF or BI data	Screening log
Unable to consent	Prospective	Paper-CRF	Screening log
Non Danish-speaking	Prospective	Paper-CRF	Screening log
Age	Retrospective	BI data	Screening log
Sex	Retrospective	BI data	Screening log
Length-of-stay	Retrospective	BI data	Screening log
After consent, only included patients			
PATIENT REGISTRATION DATA			
Site	Prospective	eCRF $	Baseline characteristics
CPR number, patient	Prospective	eCRF	Identifier
Full name, patient	Prospective	Consent form	Identifier
E-mail, patient	Prospective	Consent form	Study results information
Address, patient	Retrospective	BI data	Study results information
Telephone number, patient	Prospective	Consent form	Patient questionnaire invite
Datetime of consent	Prospective	Consent form	Study time origin
Randomization	Prospective	eCRF	Study allocation
SONOGRAPHER CHARACTERISTICS			
Name	Prospective	Sonographer survey	Baseline characteristics
Seniority (specialist, resident, etc)	Prospective	Sonographer survey	Baseline characteristics
Post-graduate years	Prospective	Sonographer survey	Baseline characteristics
Specialization	Prospective	Sonographer survey	Baseline characteristics
Ultrasound experience	Prospective	Sonographer survey	Baseline characteristics
Ultrasound education	Prospective	Sonographer survey	Baseline characteristics

	Objective lung and cardiac ultrasound competence	Prospective	Sonographer survey	Baseline characteristics
	PATIENT DEMOGRAPHICS AND CHARACTERISTICS			
	Age	Retrospective	BI data	Baseline characteristics
	Sex	Retrospective	BI data	Baseline characteristics
	Height	Retrospective	BI data	Baseline characteristics
	Weight	Retrospective	BI data	Baseline characteristics
	Co-morbidities	Retrospective	BI data + MR [§]	Baseline characteristics
	Prior admissions within the last year	Retrospective	BI data	Baseline characteristics
	Prior chest or cardiac imaging within last month	Retrospective	BI data	Baseline characteristics
	Smoking	Retrospective	BI data+ MR [§]	Baseline characteristics
	OUT OF HOSPITAL CHARACTERISTICS			
	Prehospital ultrasound	Retrospective	BI data	Baseline characteristics
	Prehospital record	Retrospective	BI data	Baseline characteristics
	General practitioner referral notes	Retrospective	BI data	Baseline characteristics
	TRIAGE AND ED METRICS			
	Arrival datetime	Retrospective	BI data	Outcomes time origin
	Chief complaints	Retrospective	BI data	Baseline characteristics
	Vital parameters	Retrospective	BI data	Baseline characteristics
	Triage color	Retrospective	BI data	Baseline characteristics
	Seen by physician	Retrospective	BI data	Baseline characteristics
	Physician responsible for patient	Retrospective	BI data	Baseline characteristics
	MEDICAL HISTORY			
	Medications	Retrospective	BI data	Baseline characteristics
	Symptoms	Retrospective	MR	Baseline characteristics
	PHYSICAL EXAMINATIONS			
	Jugular venous exam	Retrospective	MR	Baseline characteristics
	Cardiac auscultation	Retrospective	MR	Baseline characteristics
	Peripheral pulses exam	Retrospective	MR	Baseline characteristics
	Lung percussion	Retrospective	MR	Baseline characteristics
	Lung auscultation	Retrospective	MR	Baseline characteristics
	Clubbing	Retrospective	MR	Baseline characteristics
	Abnormal breathing patterns	Retrospective	MR	Baseline characteristics
	Lower extremity exam	Retrospective	MR	Baseline characteristics

	POINT-OF-CARE ULTRASOUND CHARACTERISTICS			
	POCUS performed	Prospective	1st diagnostic survey	Intervention characteristics
	POCUS duration	Prospective	Cine-loop meta-data	Intervention characteristics
	Indeterminate views	Prospective	1st diagnostic survey	Intervention characteristics
	Missed views	Prospective	1st diagnostic survey	Intervention characteristics
	Pneumothorax	Retrospective	MR	Intervention characteristics
	Focal multiple B-lines	Retrospective	MR	Intervention characteristics
	Consolidation	Retrospective	MR	Intervention characteristics
	Pleural effusion	Retrospective	MR	Intervention characteristics
	Interstitial syndrome	Retrospective	MR	Intervention characteristics
	Pericardial effusion	Retrospective	MR	Intervention characteristics
	Dilated right ventricle	Retrospective	MR	Intervention characteristics
	Left ventricular systolic contractility	Retrospective	MR	Intervention characteristics
	DP [£] CHARACTERISTICS			
	Biochemistry analyses	Retrospective	BI data	DP characteristics
	Electrocardiogram	Retrospective	BI data	DP characteristics
	Imaging	Retrospective	BI data	Outcome analyses
	Microbiology	Retrospective	BI data	DP characteristics
	Pathology	Retrospective	BI data	DP characteristics
	Performed datetime	Retrospective	BI data	DP characteristics
	Results datetime	Retrospective	BI data	DP characteristics
	HOSPITAL STAY METRICS			
	Discharging physician	Retrospective	BI data	Sub-group analyses
	Diagnosis registrations	Retrospective	BI data	Outcome variable generation
	Department and unit admissions	Retrospective	BI data	Baseline characteristics
	Datetimes of transfers	Retrospective	BI data	Baseline characteristics
	Vital parameter measurements	Retrospective	BI data	Outcome variables generation
	OUTCOMES			
	Length-of-stay	Retrospective	BI data	Outcome analyses
	Hospital contacts following 30 days	Retrospective	BI data	Outcome analyses
	Mortality	Retrospective	BI data	Outcome analyses
	Treatments	Retrospective	BI data	Outcome analyses
	Patients' experience	Prospective	Patient survey	Outcome analyses
	Number of differential diagnoses	Prospective	Diagnostic surveys	Outcome analyses
	Diagnostic pre- and post-test probabilities	Prospective	Diagnostic surveys	Outcome analyses
	Physicians' experienced benefit of testing	Prospective	Diagnostic surveys	Outcome analyses

[*]BI data = business intelligence data, [$] CRF = case report form, [§] MR = medical record, [£] DP = diagnostic pathway

8. Participant timeline

8.1 Screening and enrollment

Patients will be screened by the including physician looking through lists of patients arriving to the ED with dyspnea. During the initial assessment, and upon fulfillment of inclusion criteria, the treating physician will ask for informed consent, enroll, and randomize the patient. The exact time of randomization should be immediately after the physician's physical examination. When asked for informed consent, each patient will be provided with that amount of time for consideration she needs and given the opportunity to request an assessor (see 9.3.2) considering the acute nature of the disease.

Shifting treating ED physician is likely to happen in-between intervention and completion of the diagnostic work-up. In any case of shifting treating ED physician, this will be registered in the diagnostic survey, but data collection and study flow will continue unaltered.

8.2 Screening log

Including physicians will not be able to screen all potentially eligible patients. Therefore, all patients, at the participating sites, with a registered chief complaint of dyspnea will be retrospectively entered into a screening log, if they were not included in the study. Patients that physicians screen, will also be included in the screening log prospectively by using the paper-CRF. Patients fulfilling inclusion criteria and no exclusion criteria but who are not randomized will be deemed “inclusion failure”. Inclusion failures will continuously be monitored to access potential failure of allocation concealment and selection bias. Patients in the screening log who arrived at the ED when an including physician was present will be deemed "eligible, non-enrolled". Those patients in the screening log arriving at other timeslots, will be deemed "non-eligible due to no including physician present".

8.3 SPIRIT flow diagram: Schedule of enrolment, interventions and assessments

	STUDY PERIOD						
	Enrolment	Randomization	Post-randomization		Close-out		Follow-up
TIMEPOINT	-t1	0	t1 PA/± POCUS	Ended SDP	ED Discharge	Discharge	7-30 days
ENROLMENT:							
Eligibility screen	X						
Screening log	X						X
Informed consent		X					
Randomization		X					
INTERVENTIONS:							
POCUS-driven IP			X				
SDP			X				
ASSESSMENTS:							
Case Report Form	X	X					
Diagnostic survey			X	X			
Patient Questionnaire						X	
Retrospective data retrieval Baseline characteristics Vital parameters Biochemical findings Microbiologic findings Treatments Admission metrics (timing and units) Readmissions Mortality						X	X
Manual record review PA findings Ultrasound findings Radiologic findings						X	X

SDP=standard diagnostic pathway, PA=primary assessment

9. Ethical considerations

9.1 Clinical equipoise

9.1.1 Potential benefits

The introduction section (*1.0*) provides details on the potential benefits of a POCUS-driven diagnostic pathway. In brief, no randomized controlled trials have investigated the effect of POCUS on patient-centered outcomes, few trials have investigated POCUS as a first-line test, and no studies have verified the robustness of the secondary finding on 24-hour hospital stay found by Riishede et al.[19]

9.1.2 Potential harms

The addition of POCUS is pain- and radiation free. Ultrasound users should always be aware of the thermal and mechanical indexes, but particular care should not be taken when transthoracic ultrasound is performed in this population.[42] Incidental findings in this study can occur, but in a comparable study, the number of downstream interventions were overall non-different between groups, and rather accelerated in time than increased in number.[16] Patient discomfort from POCUS in dyspneic patients is infrequent.[43]

Based on the diagnostic decision recommendations given in the POCUS-driven intervention, patients in the intervention group can potentially be burdened by less diagnostic tests and thereby under- or misdiagnosis. The single diagnostic test that will be cut down is overridingly chest x-ray. However, based on existing diagnostic accuracy evidence, the risk for under- or misdiagnosis seems negligible given that POCUS equalizes or outperform chest x-ray in these studies. Likewise, in rare cases, when treating physicians have already implemented focused lung or cardiac ultrasound in their everyday clinical practice and patients are randomized to the control group, it can be argued that patients are burdened by this study allocation. In both scenarios, it is important to stress that the treating physician can always discontinue or modify allocated intervention if clinical deterioration and patient safety demands it.

9.1.3 Risk/benefit ratio

The diagnostic evidence from multiple diagnostic accuracy studies published on POCUS for dyspneic ED patients provide evidence that the real risk of harm or patient burdening is minimal. However, despite some solid-designed studies, the benefit from large-scale and pragmatic implementations is still unclear. The current patient risk/benefit ratio is promising and unlikely above one. However, still no evidence of clear patient-relevant benefits exists. In conclusion, there is clear clinical equipoise for the POCUS-driven diagnostic pathway for dyspneic ED patients.

9.2 Procedures

9.2.1 Ethical review committee

The trial will be approved by the regional ethics committees (case number: 1-10-72-160-22).

9.2.2 Trial-specific procedures

Patients will be asked for informed consent before enrollment and randomization. Trial information and the consent request will take place in an undisturbed room and the patient will have the opportunity to request an assessor. Between the trial information and the consent request, the patient will be provided with an appropriate amount of time for consideration with respect to the acute situation, and further time can be requested as needed. The person obtaining consent will be a member of the trial team (i.e., physician, research nurse, medical student etc.) with sufficient knowledge about the patient, the condition, and the trial.

When approached, the patient will be informed, verbally and in writing, about the background and significance of the study, inclusion criteria, potential risks and benefits, as well as a brief description of the study protocol. They will be informed that interventions only include the point-of-care ultrasound-driven diagnostic pathway and the questionnaire, and that future participation will only include data collection. The patient will then provide written informed consent utilizing the informed consent form approved by the ethical review committee. When consent is obtained from participants, information about potential de-identified data sharing will also be included.

An informed consent includes permission to obtain relevant health information on included patients from the electronic patient record obtained and accessed by study personnel as well as relevant, controlling authorities if necessary.

If a patient who has already consented, at some point denies future participation in the trial, no additional data will be collected but all data collected up until the point of withdrawal will be included consistent with Danish law.[44]

9.2.3 Insurance

The patients in the study are covered by the Danish patient insurance.[45]

10. Data monitoring

The POCUS-driven diagnostic pathway constitutes a minimal risk of harm; therefore, no periodic inspection of accumulating outcome data is planned. Good clinical practice monitoring is not mandated as the trial uses diagnostic equipment that is CE approved to the specific purpose. Participants are not subject to additional risky procedures and therefore registration to the Danish Medicines Agency is not required.

11. Timeline and Enrollment

11.1 Inclusion start and timeline

Inclusion is planned to start the 4th of January in one site (Horsens). During February to April 2023, two sites will be added each month. Inclusion rates will be determined from a sceptic approach assuming seven sites in total with three physicians per site, including one patient each, every 12 days (0.08 patients per physician-day. According to those assumptions, inclusion will be ended by the 25th of February 2024.

11.2 Recruitment

A sceptic assumption is that each physician can include a patient every 12 days and that each site will have three physicians being able to include. With this inclusion rate, 7 sites or 21 physicians can finalize inclusion by February 25, 2024 (in 421 days) and 13 sites or 39 physicians can finalize by October 23, 2023 (in 296 days). I may be that some sites have more than three competent and willing physicians and we do hope for higher inclusion rates per physician-day than 0.08. But from these brief calculations we feel confident that it will be feasible to complete study inclusion at some point in between October 2023 and February 2024.

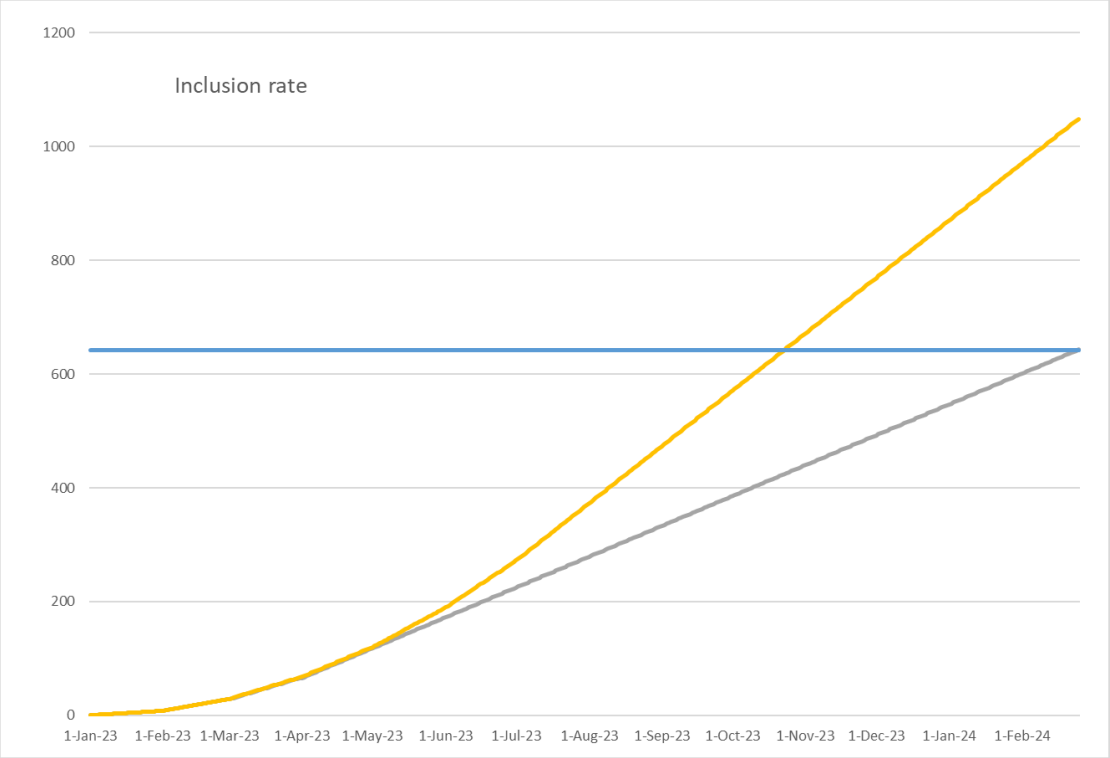

Figure 1: Blue line is sample size of 642. Grey line is 7 sites and orange line is 13 sites

11.3 International sites

Non-Danish sites can participate on the same terms as Danish sites and physicians. Local legislation must be followed, and local ethics committees consulted. Data will be kept and managed under local site facilities and data collection methods may be altered according to feasibility and available sources. Few secondary or tertiary outcomes may also be omitted in case data is not producible or clinical practice is affected. The patients' experience questionnaire will only be distributed among Danish sites.

12. Patient and public involvement

Patients and the public will not be involved in the preparation or execution of the present trial. The results will be disseminated in public and directly to involved patients by request in the written consent form.

13. Funding and economy

This investigator-initiated study is funded by the Central Denmark Region (with 1.629.000 DKK). The funding is covering wage costs for the primary investigator and are held in a research account at Horsens Regional Hospital. The primary investigator is employed at the Central Denmark region but the

sponsor has no role in designing or executing the study or interpreting, writing, or submitting the manuscript. The primary investigator declares no other conflicts of interest.

14. Publication plan

Three manuscripts are planned from the current trial. The first and primary manuscript will include the primary and secondary outcomes (see *section 5.1 and 5.2*). This manuscript will adhere to the CONSORT guidelines [46]. Results will be sought published in an international peer-reviewed journal regardless of findings (i.e., negative, positive, and inconclusive results). If any protocol amendments are necessary, they will be clarified in the final report. The principal investigator will be the first and corresponding author, and JW will be the last author. Additional authorship will follow authorship guidelines from the International Committee of Medical Journal Editors [47] and will include members of the steering committee and one site investigator per. In addition, physicians enrolling ≥ 20 patients will be offered critical manuscript revision and authorship. The trial results will be shared with participating sites and via press releases but not directly with the participating patients. The second manuscript will investigate the diagnostic thinking efficacy by focusing on the diagnostic outcomes: (1) number of differential diagnoses; (2) diagnostic pre- and post-test probabilities; (3) experienced benefit of testing from the physicians' perspective; (4) patients' experiences; (5) concurrent treatment; (6) change in diagnosis from ED contact to hospital discharge. The third manuscript will explore the effect of POCUS on measures and scores for clinical deterioration (i.e., early warning and organ failure scores).

15. Data sharing

Six months after the publication of the last results, all de-identified individual patient data will be made available for data sharing [48]. Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification of the data. Data will be completely anonymized according to Danish law.

All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties (Danish or foreign) who have approval from an independent review committee and who have a methodological sound proposal as determined by the steering committee of the current trial. Only the methodological qualities and not the purpose or objective of the proposal will be considered. Interested parties will be able to request the data by

contacting the principal investigator. Authorship of publications emerging from the shared data will follow standard authorship guidelines from the International Committee of Medical Journal Editors and might or might not include authors from the steering committee depending on the nature of their involvement.

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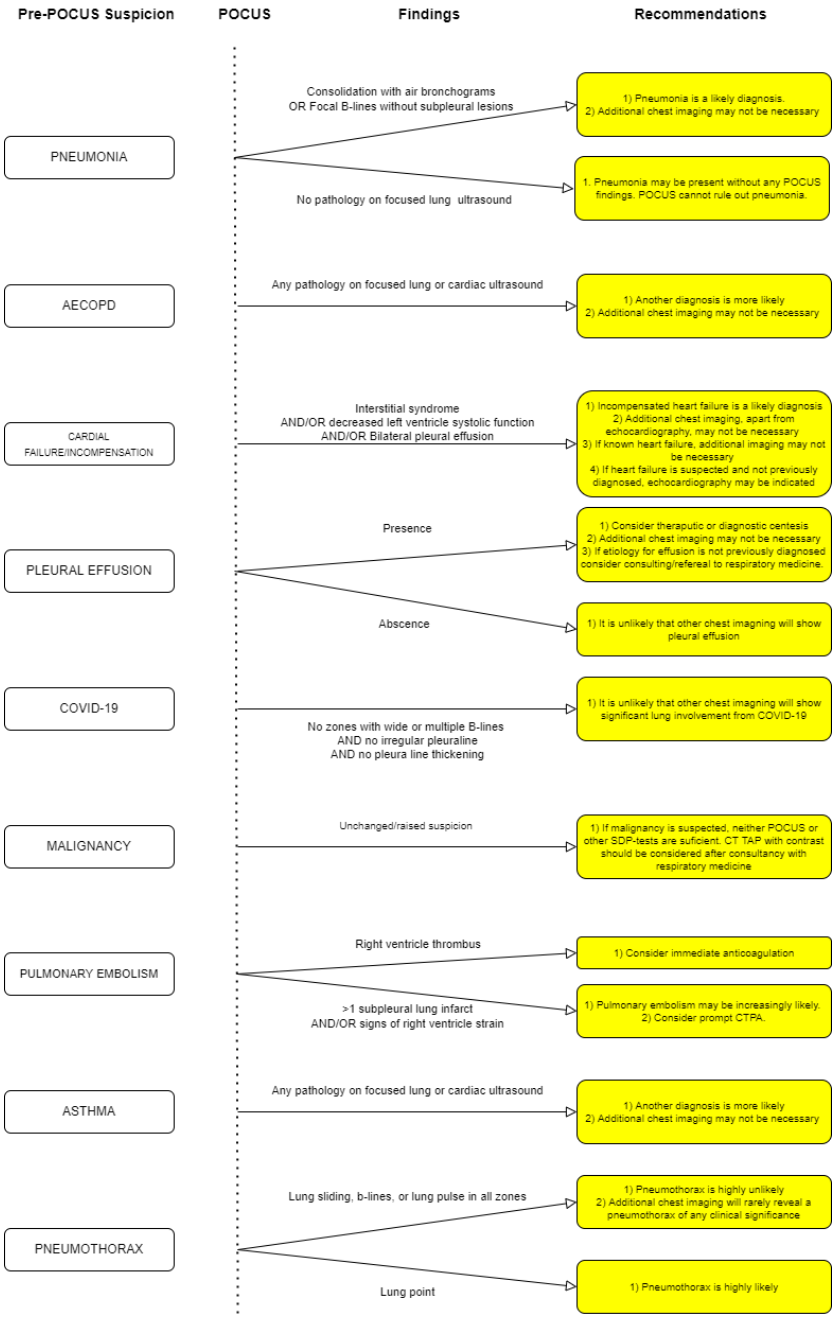
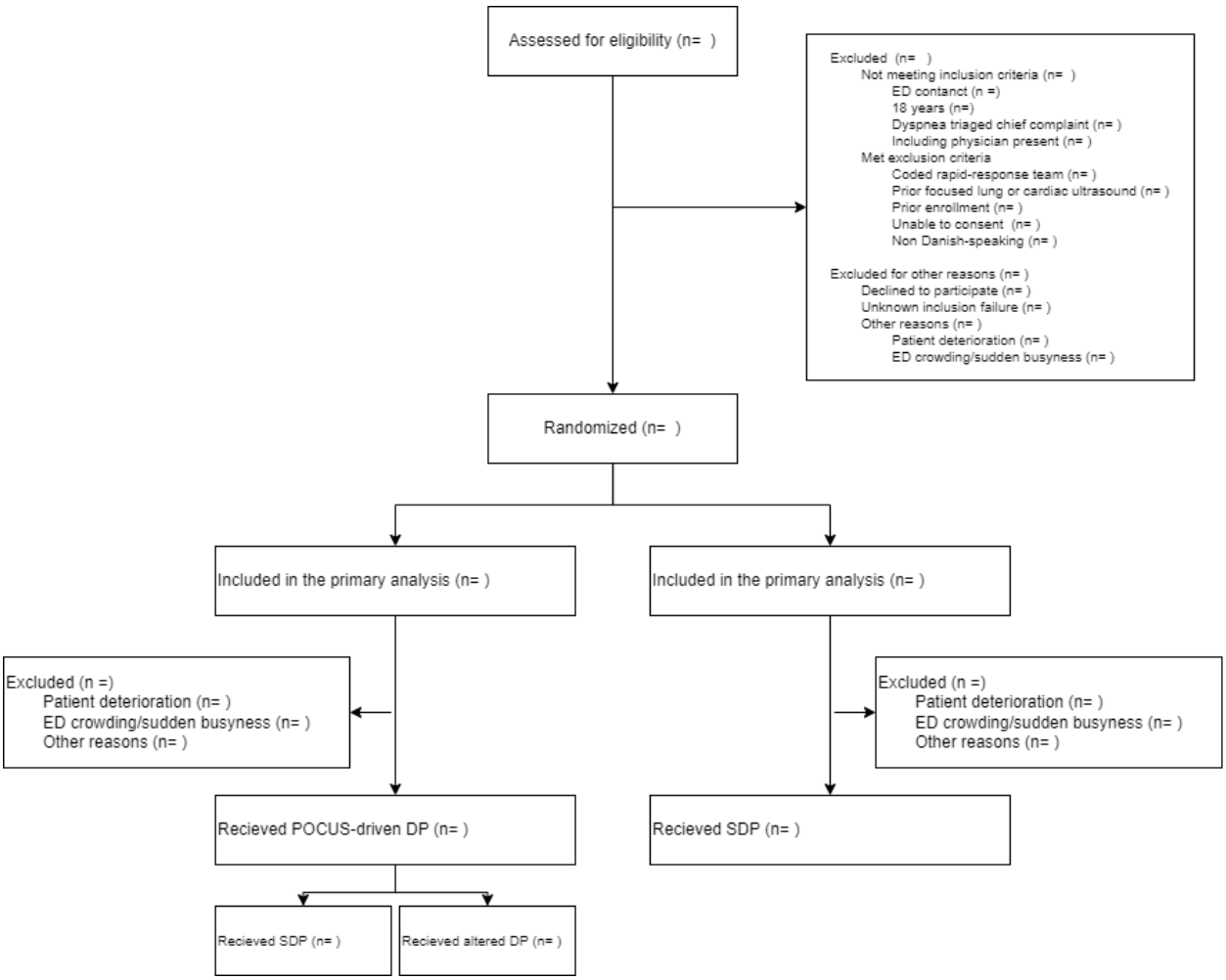
Supplementary material

Point-of-care ultrasound-driven diagnostic pathway (Diagnostic decision recommendations)



CONSORT flow diagram



Patients' experience questionnaire

Patient tilfredshed

Record ID _____

Var længden af ventetiden fra du ankom, til du blev undersøgt, acceptabel?

Svar "ikke relevant", hvis du ikke oplevede ventetid

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Var personalet venligt og imødekommende?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Spurgte personalet ind til din beskrivelse af din sygdom/tilstand?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Var du med til at træffe beslutninger om din undersgelse/behandling i det omfang, du havde behov for?

Svar "ikke relevant", hvis du ikke har behov for at træffe beslutninger

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Fik du alle de informationer, du havde behov for?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Modtog du den information, som du havde behov for i forhold til din behandling/undersøgelse?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Blev du løbende informeret om, hvad der skulle foregå?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Var den mundtlige information, du fik under dit besøg, forståelig?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Gav personalet dig tilstrækkelig information til, at du var tryg ved tiden efter dit besøg?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Er du tilfreds med den behandling, som du modtog for din sygdom/tilstand?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Er du alt i alt tilfreds med dit besøg?

◯ Slet ikke (1) ◯ I ringe grad (2) ◯ I nogen grad (3) ◯ I høj grad (4) ◯ I meget høj grad (5)
◯ Ved ikke ◯ Ikke relevant for mig

Skriv venligst her, hvis du synes,[akutmodtagelsen] kunne gøre noget bedre eller gjorde noget særligt godt:
Det, du skriver i kommentarfeltet, sendes uredigeret videre til hospitalet. Undlad at skrive personlige oplysninger såsom navn, cpr-nummer, adresse m.v.