BMJ Open

Monitoring patients with acute dyspnoea with a serial focused ultrasound of the heart and the lungs (MODUS): a protocol for a multicentre, randomised, open-label, pragmatic and controlled trial

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To cite: Arvig MD, Lassen AT, Gæde PH, *et al*. Monitoring patients with acute dyspnoea with a serial focused ultrasound of the heart and the lungs (MODUS): a protocol for a multicentre, randomised, open-label, pragmatic and controlled trial. *BMJ Open* 2020;**10**:e034373. doi:10.1136/bmjopen-2019-034373

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-034373).

Received 18 September 2019
Revised 01 May 2020
Accepted 05 May 2020

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ABSTRACT

Introduction Among patients admitted to an emergency department, dyspnoea is one of the most common symptoms. Patients with dyspnoea have high mortality and morbidity. Therefore, novel methods to monitor the patients are warranted. The aim is to investigate whether therapy guided by monitoring patients with acute dyspnoea with serial ultrasound examinations of the heart and the lungs together with standard care can change the severity of dyspnoea compared with treatment guided by standard monitoring alone.

Methods and analysis The study will be conducted as a multicentre, randomised, pragmatic, open-label and controlled trial where patients admitted with acute dyspnoea to an emergency ward will be randomised into a standard care group and a serial ultrasound group with 103 patients in each. All patients will be examined with an ultrasound of the heart and the lungs upfront. In addition, the patients in the serial ultrasound group will be examined with an ultrasound of the heart and lungs two more times to guide further therapy during the admittance. The primary outcome is a change in dyspnoea on a verbal scale. After discharge, the patients are followed for 1 year to assess the number of readmissions, death and length of hospital stay.

Ethics and dissemination The trial is conducted in accordance with the Declaration of Helsinki and approved by The Regional Committee on Health Research Ethics for Region Zealand, Denmark (identifier SJ-744). Data handling agreement with participating centres has been made (identifier REG-056–2019). The General Data Protection Regulation and the Danish Data Protection Act will be respected. The results of the trial will be reported in peer-reviewed scientific journals regardless of the outcomes.

Trial registration number NCT04091334

Strengths and limitations of this study

- First randomised trial to investigate whether therapy guided by monitoring patients with acute dyspnoea with serial focused ultrasound examinations of the heart and the lungs can changethe severity of dyspnoea compared with standard care.
- Designed as a multicentre study to improve the generalisability of the findings.
- Not powered to investigate the differences in mortality and morbidity.
- Patients are not consecutively recruited providing a risk of selection bias.

INTRODUCTION

Acute dyspnoea is a common symptom when patients are admitted to an emergency department (ED).[1] Dyspnoea is triggered by different diseases, for example, heart failure, chronic obstructive lung disease and pulmonary embolism.[2] Patients admitted with shortness of breath as the primary complaint have high in-hospital and out-of-hospital mortality.[3] Furthermore, dyspnoea is an important patient-related outcome causing anxiety among the patients.[4–6] Consequently, the evaluation and monitoring of this patient population are essential.

Monitoring the patients with acute dyspnoea is often performed by measuring vitals, scoring symptoms on different scales and analysing medical tests, for example, blood samples, chest X-ray and arterial blood gases but these approaches lack precision.[7–10] Point-of-care ultrasound can be used in both the initial diagnostic evaluation and in the monitoring of the patients with acute dyspnoea. Ultrasound examination of the inferior vena cava (IVC) either alone or as part of focused cardiac ultrasound (FoCUS) is used to evaluate if the patients are fluid tolerable judged by the diameter and the

respiratory collapsibility of the IVC.[11] Ultrasound of the IVC is also used as a diagnostic tool for the identification of congestive heart failure in patients presenting with dyspnoea.[12] Focused lung ultrasound (FLUS) can be used to diagnose interstitial syndrome (lung diseases affecting the lung interstitium, eg, lung oedema), lung consolidation, pneumothorax or pleural effusion.[13–15] In some studies, FLUS[16–20] and ultrasound of the IVC[21–23] have been used to monitor and guide therapy in patients with acute dyspnoea, but the studies were clinically heterogenic. The studies have only included patients with or suspected of heart failure and not unselected patients with dyspnoea. A few studies have been conducted with the combination of FLUS and ultrasound of the IVC but were inconclusive.[24 25]

The aim is to investigate whether therapy-guided monitoring of patients with acute dyspnoea with serial focused ultrasound examinations of the heart and the lungs can reduce the severity of dyspnoea compared with standard care.

METHODS

This study protocol is prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[26] The SPIRIT checklist is provided in the online supplementary material 1.

Study design

The trial is designed as a multicentre, randomised, controlled, pragmatic and open-label study with parallel group design with an allocation ratio at 1:1. The overall structure of the study is provided in figure 1.

Study settings

The study will take place in five different EDs in Denmark. The EDs represent a wide variety of different setups regarding logistics, patient load, time from initial assessment to admission to another ward and crowding challenges. It is anticipated that each centre will be contributing in equal amount to the study population to make the results generalisable, but the amount is not a fixed size due to the potential risk of the trial to be delayed because of different working circumstances for the investigators.

Investigators

The investigators have been recruited from project managers' (MDA) own network and on different conferences in emergency medicine. It is a prerequisite that the participating physicians are certified in focused acute ultrasound through the education provided by The University of Southern Denmark or at Aarhus University.[27 28] The courses comprise theoretical and practical education and supervision of ultrasound examinations in one's own department and with final written and practical examinations. The participating physicians have used ultrasound in their daily work for at least 3 years.

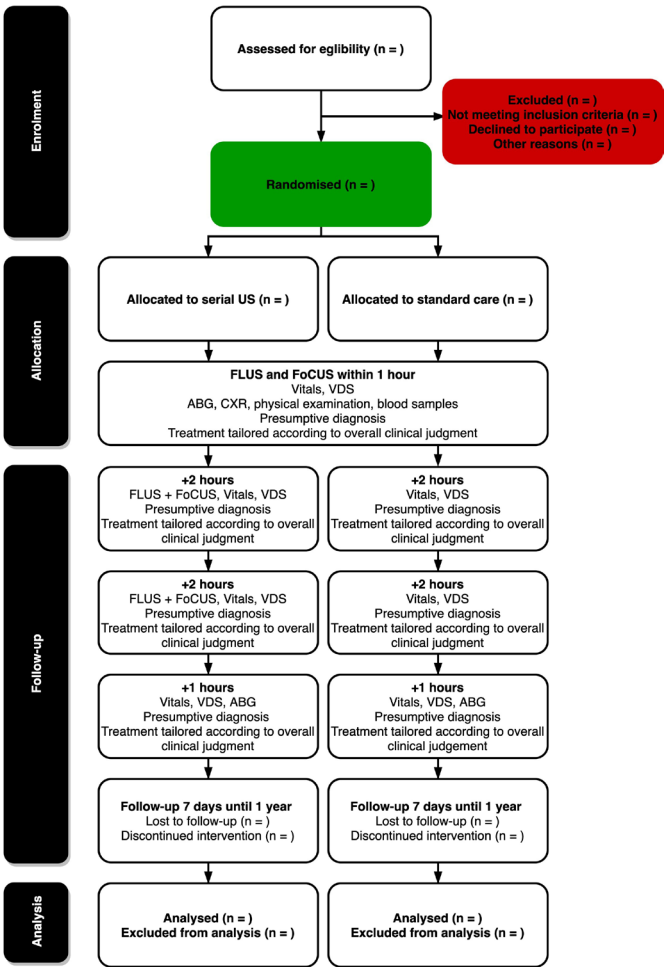

Figure 1 The flow diagram for the randomised trial. ABG, arterial blood gas; CXR, chest X-ray; ED, emergency department; FLUS, focused lung ultrasound; FoCUS, focused cardiac ultrasound; US, ultrasound; VDS, Verbal Dyspnoea Scale.

The project manager (MDA) is responsible for educating the investigators in the data collection process and the specific ultrasound protocol used in this study. This is achieved by written information and onsite presentation and demonstration of the database and the ultrasound protocol.

Eligibility criteria

Participants are recruited non-consecutively for 24 hours each day, all weekdays, to obtain a representative sample. The participants cannot be consecutively enrolled because it is not possible to have a doctor on call all the time in all centres. The investigators will do the screening, enrolment and diagnostic evaluation of the patients regardless of which study arm the patient is allocated to, thereby avoiding a different level of expertise in the treatment of the patients. The investigators will screen for potential candidate patients until an eligible patient is found. If the patient is fulfilling the eligibility criteria, which can only be achieved by asking the patients on arrival about their primary complaint, the investigator will provide the patient with oral and written information in order

to receive informed content. The reasons for exclusion from the study will be recorded. To further avoid selection bias, the randomisation is done after the screening and consent but before the first examination of the patient and allocation to the two groups. Thus, systematic differences between the groups should be avoided.

Inclusion criteria

- Participants should be 18 years or older.
- Presented at the ED with shortness of breath as the primary complaint (confirmed by asking the patient on arrival in the triage what their primary complaint is for a referral to the ED).
- Oral and written informed consent from the habile patient.
- The first evaluation of the patient including ultrasound should be performed within 1 hour from arrival to the ED.
- Have to understand Danish or English in order to provide consent.

Exclusion criteria

- Patients with dyspnoea primary admitted because of a trauma.
- If the patient is invasively ventilated within the first hour after arrival.

Randomisation

Randomisation is executed using central allocation on the online web-based database Research Electronic Data Capture (REDCap) provided by Odense Patient data Explorative Network (OPEN) at Odense University Hospital, Denmark. Permuted blocks of random numbers have been created to ensure an equal number of participants in each group. Selection bias is avoided because the allocation sequence is generated by a data manager from OPEN and because of that it is concealed from all the investigators, including the project manager (MDA). The investigators register the patient's data in the database whereby a unique identification number is received for each patient which allocates the patient to either the intervention or the control group.

Study flow

Patient enrolment is planned to start on 30 September 2019 and is expected to last for 6 months. Figure 2 provides details regarding the study flow. After arrival at the ED, patients are screened by the investigators for eligibility within 1 hour. The 1-hour limit is chosen because it is essential that the first ultrasound scan is conducted as soon as possible to avoid any treatment to influence the ultrasound findings. If the patients fulfil the inclusions criteria and are able to provide oral and written informed consent by themselves, then the patients are randomised 1:1 to either a 'serial ultrasound group' or a 'control/standard care group'.

Within 1 hour, all patients both in the 'serial ultrasound group' and the 'control/standard care group' will receive a standard physical examination, routine medical tests and an ultrasound examination of the heart and the lungs. In the serial ultrasound group, the patients will undergo, in addition to standard care, two extra ultrasound examinations of the heart and the lungs. The investigators responsible for the treatment of the patients also provide the ultrasound examinations because it is the intention that they act and titrate the treatment according to the ultrasound findings. The investigators are instructed to register the precise treatment provided. Ultrasound parameters should be interpreted together with all the other clinical information. Regarding the dynamic ultrasound parameters (B-lines, IVC and right ventricle dysfunction), the investigators are instructed as follows:

- If the patients have new onset/increased/status quo number of B-lines, the patients should be treated with diuretics adjusted to clinical scenario (eg, blood pressure) and the amount of fluid provided be stopped or decreased.
- If the IVC is flat and compressible, then give fluid.
- If the IVC is big and not compressible, then stop fluid.
- If the patients develop right ventricular dysfunction, then order D-dimer and/or CT scan directly.

In the course of admittance, the patients will have their dyspnoea registered on a Verbal Dyspnoea Scale (VDS) from 0 to 10. This scale has been validated in an acute setting and is both feasible and easy to use.[29 30] The VDS is registered by a nurse blinded to the allocation and not informed about the trial or the intervention.

Patients in both groups will be clinically evaluated at the same timepoints (2, 4 and 5 hours after initial assessment) at bedside by the investigator and changes in diagnostics and treatment will be registered.

After discharge from the hospital, the patients are followed-up for 1 year. Postdischarged data regarding death, readmissions and length of hospital stay will be accessed through the patient's electronic patient journal, or the data will be based on the Danish National Patient Registry[31] or The Danish Civil Registration System.[32] Diagnoses will be evaluated with an audit of the patient's journal according to the diagnostic criteria provided in the online supplementary material 2. The audit is performed by two independent physicians blinded to the allocation and the extra ultrasound examinations done in the intervention group (these will not be journalised). Disagreement will be resolved by a third reviewer making a consensus agreement.

Intervention: the ultrasound protocol

The ultrasound protocol consists of the following elements:

Focused cardiac ultrasound

The ultrasound of the heart is based on the international evidence-based recommendations for focused cardiac ultrasound.[33] The heart will be scanned in four views: subcostal, parasternal long axis, parasternal short axis and apical four-chamber. In the FoCUS, the following

	STUDY PERIOD									
	Enrolment	Allocation	Admission				Follow-up			
TIMEPOINTS	0	0	< 1 hour	+ 2 hours	+ 2 hours	+ 1 hours	7 days	30 days	90 days	12 months
ENROLMENT										
Eligibility screen	X									
Informed consent	X									
Allocation		X								
INTERVENTIONS										
FLUS			◆—	—	—◆					
FoCUS			◆—	—	—◆					
US of the IVC			◆—	—	—◆					
ASSESSMENTS										
Baseline variables†			X							
VDS (0-10)			X	X	X	X				
Vitals‡			X	X	X	X				
Lung auscultation			X							
Oedema§			X							
Blood tests¶			X							
ABG#			X			X				
CXR			X							
Other imaging††			X							
Treatment‡‡			X	X	X	X				
Diagnosis			X	X	X	X	X			
ICU transfer							X			
Length of stay							X			
Readmission(s)							X	X	X	X
Death							X	X	X	X

Figure 2 Schedule of enrolment, interventions and assessments according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. †Age, sex, smoker status, alcohol, medical history and medications. ‡Blood pressure, heart rate, respiratory rate, peripheral saturation and temperature. §One or both legs. ¶Haemoglobin, leucocytes, platelets, sodium, potassium, creatinine, C-reactive protein, D-dimer and troponins. #pH, PCO_2, O_2, bicarbonate, base excess and lactate. ††CT, MR, angiography and others. ‡‡Antibiotics, fluid, inhaled medication, diuretics, antihypertensive and others. ABG, arterial blood gas; CXR, chest X-ray; FLUS, focused lung ultrasound; FoCUS, focused cardiac ultrasound; ICU, intensive care unit; IVC, inferior vena cava; US, ultrasound; VDS, Verbal Dyspnoea Scale.

pathologies will be assessed: pericardial effusion, left ventricle dysfunction and right ventricle dysfunction. The diagnostic criteria are specified in the online supplementary material 3.

Ultrasound of the IVC

IVC will be scanned in the subcostal long-axis window with the patient in the semisupine position. The IVC is measured approximately 3–4 cm from the junction of the IVC into the right atrium (1–2 cm caudal to the hepatic vein). The diameter of the IVC will be measured during inpiration and expiration and the IVC Collapsibility Index (IVC-CI) will be calculated from the formula: IVC-CI = $(IVC_{max}–IVC_{min})/IVC_{max} \times 100$.

Focused lung ultrasound

The lungs will be scanned in eight zones. The anterior and lateral part of the thorax is divided into superior and inferior quadrants. Each quadrant represents a zone in which the probe shall be placed longitudinally between two ribs and create a picture of the costae and pleura. The patient will be positioned in the semisupine position, and in each zone, the patient is scanned for at least one respiratory cycle. A convex probe will preferably be used.[34] The target depth will depend on the constitution of the patient and where on the thorax the patient is scanned but a desirable depth of 18 cm will be used to evaluate the presence of B-lines. The maximum number of B-lines (dynamic ultrasound artefacts representing

interstitial syndrome) in each zone will be counted manually. Furthermore, other pathologies, for example, pleural effusion, pneumothorax and consolidations, will be assessed. The principles of the FLUS examination is based on the International Recommendations for Lung Ultrasound,[13] and the precise diagnostic criteria are provided in the online supplementary material 3.

Outcomes

Primary outcome

- Change in dyspnoea on VDS from arrival until the last evaluation is made.

Secondary outcomes for both groups

- Length of stay (consecutive days in the hospital including transfer to another ward).
- The proportion of readmissions within 7 and 30 days, 6 and 12 months.
- In-hospital all-cause mortality.
- 7-day, 30-day, 6-month and 12-month all-cause mortality after admission.
- Proportion of patients correctly diagnosed after the second and third ultrasound examinations compared with the controls receiving usual care at the same timepoints.

Secondary outcomes for the serial ultrasound group

- IVC-CI correlated to vital signs and VDS.
- B-line count correlated to vital signs and VDS.
- The dynamic changes in IVC-CI between the ultrasound examinations.
- The dynamic changes in B-line count between the ultrasound examinations.

Sample size

The sample size is calculated from the primary outcome—change in dyspnoea on a VDS. In a former study where VDS was used in the ED on patients admitted with dyspnoea, the initial median score for the admitted patients with dyspnoea was 7 on the scale from 0 to 10.[30] After the initial evaluation and treatment, it was decreased by one point. Another study supports that a one-point decrease is regarded as a minimally clinically important difference (MCID) for the patient with dyspnoea on this scale.[5] It is expected that the patients in the serial ultrasound group will achieve a greater improvement on the scale compared with the standard care group because the treatment in the ultrasound group is titrated to the ultrasound findings, which is supported by an ongoing systematic review regarding monitoring patients with serial ultrasound conducted by this research group.[35] It is anticipated by the research group that the VDS will decrease by two points in the ultrasound group compared with a 1-point improvement in the standard care group. VDS is reported as the median and interquartile range (IQR) in the former study because the data were not normally distributed. To calculate sample size, the standard deviation (SD) is estimated to be 2.42 from the reported IQR of 6–9 with the Box-Cox methods proposed by McGrath *et al*.[36] With an assumption of a power of 80%, type 1 error of 5% and 10% dropouts, the sample size is 103 patients in each group.

Statistical analysis

Baseline characteristics

Demographic and other baseline characteristics of the participants will be summarised and divided into the intervention and control group and will include: age, sex, comorbidity, smoker status, alcoholic usage, medications and the results of the first clinical assessment of the patients (VDS, lung auscultation, oedema, vitals, blood samples, arterial blood gases and ultrasound findings). Continuous variables will be summarised as means and SD or medians and IQR depending on the distribution of the variables. For categorical variables, frequencies and percentages will be reported. Where values are missing, percentages will be calculated for the available cases and the denominator will be mentioned.

The primary outcome

The primary outcome—change in dyspnoea on VDS—will be compared between the two groups to detect any difference. Pairwise comparisons of VDS will be made at the same timepoints in both groups.

The secondary endpoints

Length of stay, death and the number of readmissions will be registered in the follow-up of the patients. Comparisons between the two groups will be made to detect a difference. Time to event (dead or readmission) will be visualised with Kaplan-Meier curves. Cox regression will be used to analyse whether there is an association related to the UL findings when adjusting for diagnosis and age. In the case of lost to follow-up or other reasons for missing data, both intention-to-treat and per-protocol analysis of the predefined outcomes will be used to allow readers to interpret the effectiveness of the therapy guided by the ultrasound intervention.

The secondary endpoints registered in the serial ultrasound group

The dynamic changes in IVC-CI and sum of B-lines will be expressed as means and SD or median and IQR depending on the distribution of the data and compared between the different timepoints where the parameters are registered (figure 2). Furthermore, IVC-CI and the sum of B-lines will be compared with vitals and VDS score to detect a correlation.

The intraobserver and interobserver variabilities will be assessed with 10% of the included patients. The scans will be stored and anonymised. Afterwards, they will be reanalysed by the same investigator with a minimum interval of 30 days and then by a second investigator. The variability will be assessed with Cohen's kappa.

All statistical analyses will be performed with STATA V.15.0.

Data management

The registered data on each patient will be directly recorded and securely stored in an encrypted, logged

and password-protected database REDCap. The database is created by the project manager (MDA) together with a data manager from OPEN. All adjustments in the database are logged. In this database, each patient receives a unique identification number securing patient identity. The investigators will gain access to this database to withdraw a randomisation number and to enter data. All the data reported are linked to each specific investigator. The randomisation process is concealed to all the investigators and the database creator.

A data monitoring committee is not appointed because focused ultrasound is free from radiation and pain and carries no potentially harmful consequences for the patients.[37] No interim analyses or endpoint adjustments are planned. The trial is planned to end when the last included patient has been followed for 1 year. Any decision to end the trial before this point will be made in cooperation and full agreement between the project manager (MDA), and the supervisors (ATL, PHG and CBL).

Patient and public involvement

Patients and the public were not involved in the design and development of the study. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. During and after the trial, the patients are invited to respond to the setup of the trial and to the patient's comfort or discomfort during the interventions. The responses will be taken into consideration for possible adjustments. The results of the trial will be disseminated to the involved patients by request, which is applied to the informed content material the patients are receiving.

ETHICS AND DISSEMINATION

The ultrasound examination is safe to use.[37] The study will be conducted in accordance with the Declaration of Helsinki.[38] Patient autonomy is respected and written consent is obtained before enrolment in the study. The patients can at any point withdraw their consent. The study is approved by The Regional Committee on Health Research Ethics for Region Zealand, Denmark (identifier SJ-744). A data handling agreement with OPEN, University of Southern Denmark, has been signed. The centres participating in the project have approved the data handling process. The study has been approved for data storage by the Region Zealand, Denmark, and is registered on the Region Zealand Register of Trials (identifier REG-056–2019). All data are stored, secured and managed according to the laws and regulations in the General Data Protection Regulation (GDPR)[39] and the Danish Data Protection Act.[40] The trial is registered on ClinicalTrials.gov. In the events of important modifications or adjustments to the trial protocol, the relevant institutions will be informed and amendments will be registered on ClinicalTrials.gov.

The results of this trial will be conducted following the Consolidated Standards of Reporting Trials statement[41] in peer-reviewed scientific journals regardless of the outcomes and will have the following order of authors: MDA, ATL, PHG and CBL. The investigators involved in the trial will be offered authorship if they are interested and fulfil all the ICMJE authorship requirements. Furthermore, the results will be communicated at conferences in emergency medicine and in EDs nationally as well as internationally.

DISCUSSION

It is anticipated that the results of the study will provide clinical information from the serial ultrasound examinations together with the standard evaluation to further reduce the severity of dyspnoea of the admitted patients and thereby determine in which clinical scenarios a serial ultrasound assessment is clinically relevant to perform. This is to our knowledge the first multicentre trial investigating the value of serial ultrasound examinations in monitoring patients with acute dyspnoea.

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Acknowledgements Sample size calculations were performed in cooperation with biostatistician Sören Möller, PhD, associate professor, OPEN, University of Southern Denmark, and Department of Clinical Research, University of Southern Denmark. The acronym MODUS for the study is created by Sara Stage Voetmann, BMid, MSc in Health Science.

Contributors MDA is the principal investigator and in charge of all aspects of database management, education and information of the trial to the involving investigators; conceived the trial and received inputs and feedback from ATL, PHG and CBL; drafted the study protocol manuscript. All co-authors read and approved the final manuscript.

Funding The trial is supported by the Department of Emergency Medicine at Slagelse Hospital and by grants from the Naestved, Slagelse and Ringsted Hospitals' Research Fund (grant number111.2219) and by a 1 year scholarship from the University of Southern Denmark.

Disclaimer The funders have no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of manuscripts or in decisions to publish results.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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