Drainage Of Pleural Effusions in the Intensive Care Unit (DOPE-ICU) – feasibility trial

Drainage of pleural effusions in *the intensive care unit in adults with respiratory failure: A randomised clinical feasibility trial of performing versus withholding pleural drainage*

Protocol version 1.10, 08 November 2024

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Applicable protocol registration numbers: ClinicalTrials.gov (NCT06709456), Committee on Health Research Ethics in the North Denmark Region (N-20240027).

In drafting of the present protocol Copenhagen Trial Unit's Standard Operating Procedures were used.

Abstract

Background: Pleural effusions are prevalent in intensive care unit (ICU) patients and therapeutic ultrasonography-guided pleural drainage a common procedure, especially in adult ICU patients with respiratory failure. Therapeutic pleural drainage has been associated with improved oxygenation and ventilatory parameters, but not improvements in clinical outcomes. Furthermore, pleural drainage is an invasive procedure that carries risks of adverse events, including bleeding, pneumothorax, and potentially increased morbidity and mortality. Overall, the evidence base supporting therapeutic pleural drainage in adult ICU patients with respiratory failure is limited and no randomized clinical trials exist.

Objectives: To assess the feasibility of evaluating the effects and safety of therapeutic pleural drainage in adult patients with pleural effusion and respiratory failure in the ICU.

Design: This is an investigator-initiated, pragmatic, multicentre, open label, randomised parallel group feasibility trial.

Inclusion and exclusion criteria: All patients fulfilling all the following inclusion criteria will be screened for eligibility in the electronic case report system: (1) acutely admitted to the ICU, (2) ≥ 18 years of age, (3) pleural effusion ≥ 2 cm in either pleural cavity assessed by ultrasonography, computed tomography or magnetic resonance imaging, and (4) respiratory failure defined as one or more of the following: any oxygen supplementation in an open system, invasive or non-invasive mechanical ventilation (including non-intermittent mask continuous positive airway pressure), or an arterial partial pressure of carbon dioxide ($PaCO_2$) > 6.0 kPa and pH < 7.35 on the most recent arterial blood gas (ABG) analysis.

Patients will be excluded if they fulfil one or more of the following criteria: (1) mediastinal drain or pleural drain in situ on either side, (2) suspected or confirmed haemothorax, (3) suspected or confirmed pneumothorax, (4) suspected or confirmed pleural empyema, (5) suspected or confirmed pleural malignancy, (6) antithrombotic treatment or coagulation deficiency incompatible with conducting pleural drainage, and contraindications to reversal of this, (7) indication for therapeutic pleural drainage as per the treating clinician and (a) invasive or non-invasive mechanical ventilation or mask CPAP with arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤ 13.3 kPa in the most recent ABG analysis, or (b) high-flow humidified oxygen therapy with a flow ≥ 50 L/min and a PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis, or (c) persistent respiratory acidosis with a pH < 7.25 and a $PaCO_2$ > 6.0 kPa on the most recent ABG analysis in spite of non-invasive ventilation for > 1 hour, (8) withdrawal from active therapy or brain death deemed imminent, (9) expected ICU stay < 24

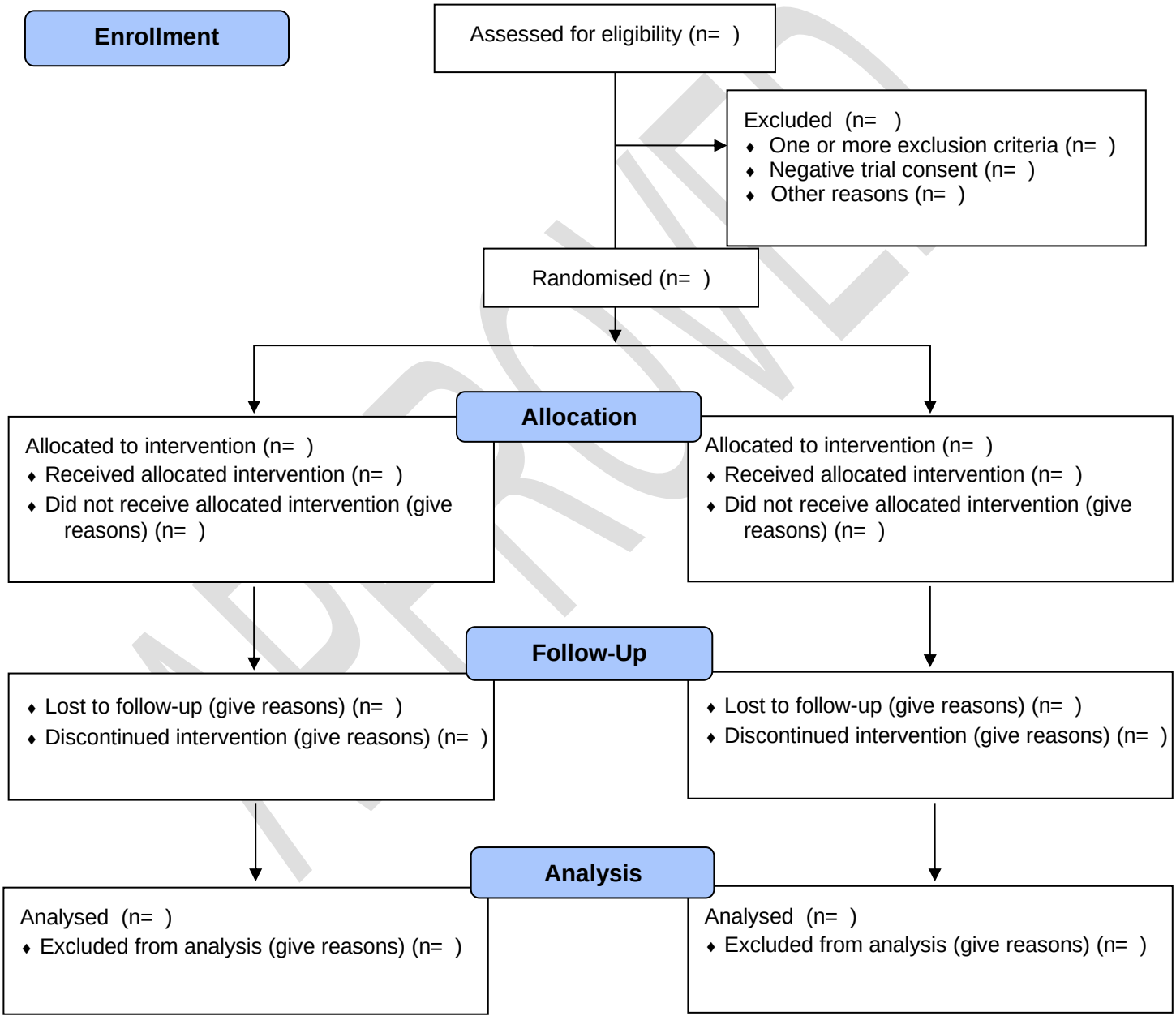
hours from randomisation, (10) pregnancy, (11) under coercive measures, (12) unobtainable consent for trial participation, or (13) previously randomised in the DOPE-ICU feasibility trial.
Intervention: Ultrasonography-guided therapeutic pleural drainage with insertion of a small-bore catheter in the pleural cavity with effusion ≥ 2 cm (uni- or bilaterally). Repeated drainage of secondary effusions during ICU stay, including readmissions, in 90 days.
Control: No therapeutic pleural drainage during ICU stay, including readmissions within 90 days, except if escape criteria are present, which are defined similarly as exclusion criteria 2,3,4,5 and 7.
Outcomes: Primary outcome (feasibility): proportion of patients receiving pleural drainage during ICU stay within 90 days from randomisation. Secondary feasibility outcomes: proportion of patients with one or more protocol violations, proportion of included patients out of the number of eligible patients, and proportion of randomised patients with consent withdrawn for use of data. Secondary clinical outcomes: all-cause 90-day mortality, number of patients with one or more serious adverse events within 90 days, absolute number of days alive without life support in 90 days, absolute number of days alive and out of hospital in 90 days. Secondary process outcomes: new pleural infection in the 90-day period, and PaO_2/FiO_2 ratio, pH, and $PaCO_2$ in ICU in the ABG analyses closest to 24 and 72 hours post-randomisation, respectively.
Trial size: A total of 88 patients are needed to detect or reject an expected 75% relative increase (an absolute increase of 30 %-points) in the primary feasibility outcome of patients receiving pleural drainage in the intervention group, assuming a maximal incidence of pleural drainage in the ICU within 90 days of 40% in the control group (two-sided $\alpha=0.05$ and $\beta=0.20$) and a maximum dropout rate of 5%.
Time schedule:
2023 – November 2024: Governance approval applications, education of trials sites, other preparations.
November 2024: First patient enrolled.
July 2025: Last patient enrolled.
October 2025: Follow-up completed.

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Trial flow chart

Acccording to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.[1].

The flowchart (n=) will be filled in at the end of the trial.



Administrative information

Sponsor, Principal Investigator and Trial Initiator

Olav Lilleholt Schjørring, MD, PhD
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Hobrovej 18-22, 9000 Aalborg
E-mail: o.schjoerring@rn.dk
Telephone: +45 9766 1921

Coordinating Investigator

Marie Schjødt Worm, MD, PhD student
Department of Anaesthesia and Intensive Care
Aalborg University Hospital

Trial Statistician

Niels Henrik Bruun, MSc
Department of Epidemiology and Biostatistics
Aalborg University Hospital
Denmark

Trial sites

Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark
Site Investigator: Marie Schjødt Worm, MD, PhD student

Intensive Care Unit 4131
Rigshospitalet, Copenhagen University Hospital
Denmark
Site Investigator: Morten Hylander Møller, MD, PhD

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Department of Anaesthesiology and Intensive Care Medicine,
Sygehus Lillebælt, Kolding
Denmark
Site Investigator: Anne Craveiro Brøchner, MD, PhD

Department of Anaesthesia and Intensive Care
Zealand University Hospital, Køge
Denmark
Site Investigator: Lars Peter Kloster Andersen, MD, PhD

Department of Anaesthesia and Intensive Care
Zealand University Hospital, Roskilde
Denmark
Site Investigator: Henrik Planck Pedersen, MD

Department of Anaesthesia and Intensive Care
Nordsjællands Hospital, University of Copenhagen, Hillerød
Denmark
Site Investigator: Morten Heiberg Bestle, MD PhD

Additional trial sites await.

Steering Committee

Olav Lilleholt Schjørring, MD, PhD
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark

Marie Schjødt Worm, MD, PhD student
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark

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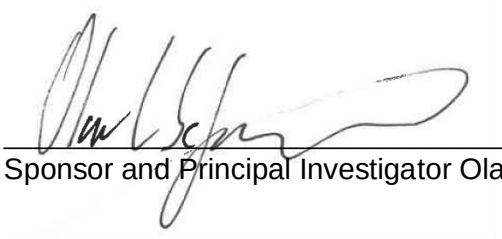
Bodil Steen Rasmussen, MD, PhD
Department of Anaesthesia and Intensive Care
Aalborg University Hospital
Denmark

Morten Hylander Møller, MD, PhD
Intensive Care Unit 4131,
Rigshospitalet, Copenhagen University Hospital
Denmark

Niels Henrik Bruun, MSc
Department of Epidemiology and Biostatistics
Aalborg University Hospital
Denmark

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Signatures



Sponsor and Principal Investigator Olav Lilleholt Schjørring, MD, PhD

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List of abbreviations

ABG: arterial blood gas

AE: adverse event

ARDS: acute respiratory distress syndrome

CONSORT: CONsolidated Standards Of Reporting Trials

CPAP: continuous positive airway pressure

CRIC: Collaboration for Research in Intensive Care

CT: computed tomography

DOPE-ICU: Drainage Of Pleural Effusions in the Intensive Care Unit

eCRF: electronic case report form

FiO_2: fraction of inspired oxygen

ICU: intensive care unit

MAP: mean arterial pressure

MRI: magnetic resonance imaging

$PaCO_2$: partial pressure of arterial carbon dioxide

PaO_2: partial pressure of arterial oxygen

REDCap®: Research Electronic Data Capture®

SAE: serious adverse event

SMS-ICU: Simplified Mortality Score for the Intensive Care Unit

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1. Introduction and background

1.1 The patient population

Respiratory failure requiring Intensive Care Unit (ICU) admittance represents a significant burden with 13 to 20 million patients requiring mechanically ventilation annually in ICUs worldwide.[2] Pleural effusion is an excessive fluid accumulation in the pleural cavity surrounding the lung and may affect respiratory function. It is produced by the parietal circulation and is continuously reabsorbed by the lymphatic system. A pleural effusion develops when the rate of pleural fluid production exceeds the rate of reabsorption.[3] The reported prevalence of pleural effusion in ICU patients is between 31% and 81% for ultrasonographically confirmed diagnosis.[4–8] Pleural effusion may be related to disorders of the lung or pleura, or to systemic disorders including fluid overload, and common causes for pleural effusion in ICU patients are congestive heart failure, pneumonia, malignancies, hepatic hydrothorax, and nephrotic syndrome.[9] Pleural effusion may contribute to the severeness of respiratory failure, as it has been associated with restrictive ventilatory impairment, hypoxaemia,[10] and failure in weaning from mechanical ventilation.[11] Additionally, it has been associated with increased mortality.[11,12]

1.2 Current treatment (or current practice)

Recent guidelines have been published by the British Thoracic Society on pleural diseases with recommendations of management of pleural effusions.[13] However, these do not issue recommendations on whether or when to conduct therapeutic pleural drainage, unless pleural infection or malignancy is suspected. In ICU patients pleural effusion has been considered clinically relevant when ultrasonographically assessed pleural separation was ≥ 2 cm in combination with a potential adverse effect on patient progress and consequently, this has been suggested as a cut-off for conducting therapeutic pleural drainage.[14] Criteria that clearly define clinical significance of pleural effusion in ICU patients and indications for therapeutic pleural drainage are, however, lacking.[15] Nevertheless, drainage of pleural effusion through ultrasonography-guided insertion of a small bore catheter is frequently conducted in ICU patients, typically to improve respiratory parameters, i.e., for therapeutic reasons,[16] with a recent Danish observational study in 81 patients finding that 40% of ICU patients with pleural effusion above 2 cm received pleural drainage during ICU admission.[8]

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1.3 Trial interventions

The DOPE-ICU feasibility trial investigates ultrasonography-guided therapeutic pleural drainage with insertion of a small-bore catheter in the pleural cavity with effusion ≥ 2 cm (uni- or bilaterally) compared with no pleural drainage in ICU patients with respiratory failure.

1.3.1 Clinical data on the experimental intervention, pleural drainage

A recent systematic review with meta-analysis on pleural drainage in ICU patients with pleural effusion identified a total of 31 observational studies on the subject, including a total of 2265 patients;[17] pleural drainage was associated with an increased partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio and end-expiratory lung volumes. Notably, no randomized clinical trials have been conducted on the subject, and therefore associations seen in the included studies may not be causal. Additionally, data on associations with patient-important outcomes such as mortality, duration of mechanical ventilation, and ICU or in-hospital lengths of stay are sparce and pleural drainage in patients with pleural effusion in the ICU have paradoxically been associated with adverse effects on these outcomes.[12]

1.3.2 Clinical data on the control intervention, no pleural drainage

Given that only 40% of patients with pleural effusion in the ICU receives pleural drainage,[8] the majority of pleural effusions are handled without drainage. Since no guidelines for whether or when to drain pleural effusions, except when pleural infection or malignancy is suspected or present, exists,[13] and since pleural drainage in ICU patients with pleural effusion has been associated with adverse effects on patient important outcomes,[12] refraining from drainage in these patients can be considered safe.

1.4 Risks and benefits

Pleural drainage is generally considered a safe procedure, especially when conducted with per-procedural ultrasonographical guidance, as recommended.[13] However, the clinical benefit from this procedure is unclear. Adverse events includes pneumothorax, haemothorax, and pleural infection, are all considered rare but potentially serious; occurrence of pneumothorax has a frequency of 0.8% after pleural drainage of ICU patients,[17] likely even lower with ultrasonographical guiding,[17,18] similarly, haemothorax has an occurrence of 0.6%.[17] Data on the risk of pleural infection after ultrasonographical pleural drainage in ICU patients is scarce, however, the risk in the overall hospital population in a national British audit was only 0,1%.[19]

Since no randomized clinical trials on the subject exists,[17] neither performing therapeutic pleural drainage nor refraining from this is proven the best strategy. Likewise, since it is unclear whether patients profit from drainage of pleural effusions, the balance between benefits and harms in either arm cannot be known with the present available evidence but need to be elucidated in the setting of a large randomized clinical trial. Therefore, there will be no additional risk for patients included in the DOPE-ICU feasibility trial.

1.5 Trial rationale and ethical justification

1.5.1 Trial rationale

Observational studies have proven that therapeutic pleural effusions in patients admitted to the ICU are frequent.[4–8] Therapeutic ultrasonography-guided drainage of pleural effusions is commonly conducted to improve respiratory parameters, especially in patients with respiratory failure, although clinical practice varies extensively.[8,16,17] Pleural drainage is associated with improvements in oxygenation and ventilator parameters,[17] but have paradoxically also been associated to adverse effects on patient-important outcomes. Therefore the balance between potential benefit and harm from therapeutic pleural drainage is uncertain.[12] In the light of how prevalent ultrasonography-guided pleural drainage in the ICU is, the complete lack of randomised clinical trials and thus solid evidence on the subject is striking.[17] A fact, which is underlined by the lack of clinical guidelines on whether or when to conduct therapeutic pleural drainage in non-infectious or non-malignant pleural effusions.[13] These points underline the need of large randomised clinical trials on performing versus withholding pleural drainage in ICU patients with respiratory failure and pleural effusion, however, since no randomised data exists, a smaller feasibility trial is obligate to ensure feasibility of the protocol and adequate separation in the intervention received between the intervention groups, while supplying preliminary data on patient-important outcomes and safety, to inform trial design in a subsequent adequately powered large randomised clinical trial to ultimately inform clinical practice. Thus, the DOPE-ICU feasibility trial represents an important step in the process of improving care of ICU patients with acute respiratory failure.

1.5.2 Ethical justification

The trial is justified, since it is in the interest of future patients and society, to establish whether pleural drainage does in fact improve mortality or other patient-important outcomes such as duration of mechanical ventilation. The individual patient may benefit from participating in the

DOPE-ICU feasibility trial as this will lead to increased focus on the patient. Future patients will benefit from the trial results, regardless of the direction of the effects, as the results will enable conduction of an adequately powered subsequent randomised clinical trial to inform clinicians on the optimal strategy for therapeutic pleural drainage in the ICU. If therapeutic ultrasonography-guided pleural drainage is not found superior to withholding such, future patients will benefit from this by avoiding the potential harms of pleural drainage, and society by the reduced costs of not conducting such.

ICU patients are temporarily incompetent because of severe illness or as a consequence of the treatment received at ICU admission and during the entire ICU stay. We cannot perform the trial in competent patients because causes of non-infectious, non-malignant pleural effusion in less sick (and thus competent) patients differs and is clinically less of an issue compared to pleural effusion in the critically ill patient in the ICU with respiratory failure.

Consent will be obtained according to national regulations for temporarily incompetent patients, which in Denmark is by proxy (see section 9.1.2 *Procedures for informed consent*). Informed consent will be obtained as soon as possible after enrolment from one independent physician (the trial guardian) and from the patient's next of kin. The trial guardian will be appointed by the local site investigator and will be a doctor, who is independent of the trial, who has knowledge of the clinical condition, and who is familiar with the trial protocol to such an extent that he or she can judge for each patient if it will be reasonable for the patient to participate in the trial. The consenting party will be provided with information about the trial, so he/she is able to make an informed decision about participation.

ICU admission with respiratory failure is an acute, life-threatening situation, and pleural drainage is performed as soon as possible after detection of pleural effusions with indication for drainage in these patients. Typically, this involves immediate referral to the Department of Radiology for bedside ultrasonography-guided pleural drainage conducted within hours from detection, or immediately by ICU physicians, depending on local practice. In some cases, a delay for up to 24 hours may be necessary to allow reversal of antithrombotic treatment or correction of coagulation deficiencies before drainage. However, in such cases, immediate action is still required, including the cessation of additional antithrombotic treatment or administration of relevant reversing agents or transfusion of plasma, platelets, or coagulation factors, to enable drainage to be conducted as soon as possible. Therefore, the intervention or related actions cannot be delayed for patients to obtain vicarious consent from the next of kin prior to enrolment, and so, the trial is considered an acute interventional trial and follows Danish regulations for trials in acute situations in temporarily incompetent patients, with subsequent consent

obtainment. Consent from the patient's next of kin and the trial guardian will be obtained as soon as possible after enrolment. The consenting party will be provided with written and oral trial information. We will obtain oral and written consent in person from next of kin if they are present. In cases where next of kin cannot be present, oral consent can initially be obtained over the phone and documented in the patient's file, with written information and consent obtainment in person as soon as possible hereafter. Patients, who regain competence, will be asked for informed consent as soon as possible. Written information and the consent form will be subjected to review and approval by the ethical committee system according to Danish law. The consenting party can at any time without further explanation withdraw consent.

1.6 Trial conduct

The DOPE-ICU feasibility trial will be conducted in compliance with this trial protocol, the Helsinki Declaration in its latest version,[20] the good clinical practice guidelines,[21] and national Danish laws. The protocol has been written in accordance with the SPIRIT 2013 Statement.[22] Enrolment will start after approval by The Committee on Health Research Ethics in the North Denmark Region and after trial registration at ClinicalTrials.gov. The trial will be registered in the North Denmark Regional research registry as required according to the Danish Data Protection agency.

No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible.

We will submit a manuscript with main points of the protocol including description of design, rationale and statistical analysis plan to a peer-reviewed medical journal.

2. Trial objectives and purpose

The objective of the DOPE-ICU feasibility trial is to assess the feasibility of evaluating the effects and safety of therapeutic pleural drainage in adult patients with pleural effusion and respiratory failure in the ICU. The primary hypothesis is that it will be possible to separate the proportion of patients receiving pleural drainage in the ICU within 90 days in the two intervention groups, meaning that a trial of randomised allocation to performing versus withholding pleural drainage in adult patients with pleural effusion and respiratory failure in the ICU is feasible. The secondary hypothesis is that pleural drainage may have an effect on patient-important outcomes.

3. Trial design

3.1 Trial design

The DOPE-ICU feasibility trial is an investigator-initiated, pragmatic, multicentre, open label, randomised parallel group feasibility clinical trial with computer generated allocation sequence, centralised and stratified allocation, and blinding of statisticians. Adult patients with pleural effusion and respiratory failure acutely admitted to ICUs in Denmark will be randomised to ultrasonography-guided pleural drainage versus withholding of such.

3.2 Randomisation

Patients will be screened for enrolment as soon as possible after all inclusion criteria are fulfilled. This will be ensured through thorough implementation of trial methodology at trial sites.

Eligible patients will be randomised 1:1 centrally through a web-based electronic case report form (eCRF) system in Research Electronic Data Capture (REDCap®)[23] according to computer-generated allocation sequence lists using permuted blocks of varying sizes and stratified according to trial site as per International Conference on Harmonisation of Good Clinical Practice.[24] The allocation sequence lists are automatically generated and concealed in the REDCap® system and are thus unknown to patients, clinicians, and trial investigators. Each patient will be allocated a unique patient-screening number.

3.3 Blinding

The allocation group will not be blinded for the investigators and clinicians as the intervention is obvious, sham drainage is impractical, and the presence of a pleural catheter in situ will and should be common knowledge in the ICU given the possible clinical implications, especially in patients receiving positive pressure mechanical ventilation. Mortality assessments will be registry-based where possible. The primary statistical analyses of the primary outcome will be done with the intervention groups masked, i.e., randomly coded as 0 and 1. Similarly, the primary statistical analyses of all secondary outcomes will be done with the intervention groups masked, and without access to the primary outcome.

3.4 Participant timeline

We will strive to screen and enrol patients in the eCRF system as soon as they fulfil all inclusion criteria. The participants will continue in the allocated intervention group until they are

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discharged from the ICU with a maximum of 90 days after randomisation. If the patient is readmitted to the ICU within 90 days after randomisation, pleural effusions will be handled as according to the allocated intervention.

4. Selection of participants

All patients referred to a participating clinical trial site will be assessed for eligibility. To ensure timely identification of eligible patients daily ultrasonographic examinations of pleurae in patients with respiratory failure will be encouraged. Patients will be eligible for randomisation if they comply with the inclusion and exclusion criteria below. We will screen all patients fulfilling the inclusion criteria in the eCRF.

4.1 Inclusion criteria

The following criteria must be fulfilled:

- Acute admission to the ICU.
- Age ≥ 18 years.
- Pleural effusion ≥ 2 cm in either pleural cavity assessed by ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) (measured between the parietal and visceral pleura perpendicularly to the chest wall at the largest-separation point. For ultrasonographic assessment, we recommend assessing pleural fluid in a transverse section perpendicular to the body axis at the lung basis along a perpendicular line between the parietal and visceral pleurae at the largest pleural separation point with the patient in supine position and a 15 ° elevation of the torso).
- Respiratory failure defined as one or more of the following: any oxygen supplementation in an open system, invasive or non-invasive mechanical ventilation (including non-intermittent mask CPAP), or most recent arterial blood gas (ABG) analysis with arterial partial pressure of carbon dioxide ($PaCO_2$) > 6.0 kPa and pH < 7.35.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria will be excluded:

- Mediastinal drain or pleural drain in situ on either side.
- Suspected or confirmed haemothorax (e.g., due to recent thoracic trauma or intrathoracic surgery).

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- Suspected or confirmed pneumothorax (e.g., by anamnesis, on radiographic or ultrasonographic assessment, or by clinical presentation, e.g., due to presence of subcutaneous emphysema).
- Suspected or confirmed pleural empyema (e.g., by anamnesis or clinical presentation, or on CT, MRI or ultrasonographic assessment).
- Pleural malignancy (suspected or confirmed pleural lymphoma, pleural metastases or direct pleural invasion, or malignant mesothelioma).
- Antithrombotic treatment or coagulation deficiency incompatible with conducting pleural drainage as by local recommendations, and contraindications to reversal of this (clinical assessment).
- Clinically assessed absolute indication for therapeutic pleural drainage and:
    - invasive or non-invasive mechanical ventilation or mask CPAP with PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis.
    - high-flow humidified oxygen therapy with a flow ≥ 50 L/min and a PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis.
    - persistent respiratory acidosis with a pH < 7.25 and a $PaCO_2$ > 6.0 kPa in the most recent ABG analysis in spite of non-invasive ventilation for > 1 hour.
- Withdrawal from active therapy or brain death deemed imminent.
- Expected ICU stay < 24 hours from randomisation.
- Pregnancy (in females < 60 years of age, non-pregnancy must be confirmed by a negative urine or plasma human chorionic gonadotropin, or presence a condition incompatible with pregnancy, e.g., previous hysterectomy, or conducted caesarean section during current hospitalisation).
- Under coercive measures (i.e., ongoing involuntary hospital admission or under correctional authorities' jurisdiction).
- Consent not obtainable as per Danish legislation.
- Previously randomised in the DOPE-ICU feasibility trial.

4.3 Participant discontinuation and withdrawal

4.3.1 Discontinuation and withdrawal at the choice of the participant or proxy

The procedure of handling withdrawal of consent from a patient will follow Danish regulations: A patient, who no longer wishes to participate in the trial can withdraw consent at any time without need of further explanation and without consequences for further treatment. If a patient is still incapacitated, withdrawal from the trial at any time can be conducted if consent is

withdrawn by the person(s) who have given proxy consent. To limit the amount of missing data we plan to keep and collect as much data from each withdrawn patient as possible. Therefore, if possible, the investigator will ask the patient from which aspects of the trial he/she wishes to withdraw from:

- Receiving the trial intervention only (allowing all data registration and follow-up).

OR

- Receiving the trial intervention AND further registration of daily and/or follow-up data.

Only the trial participant can demand deletion of already registered data and only if the participant did not consent previously. If so, all data will be deleted, and a new participant will be enrolled to obtain the full sample size.

4.3.2 Discontinuation and withdrawal at the choice of the investigator

Clinicians or investigators may deviate from the allocated pleural drainage strategy at any time, if:

- The participant experiences intolerable adverse events suspected to be related to the allocated strategy.
- The clinicians in conjunction with the coordinating centre decide it to be in the interest of the participant.
- The participant after inclusion is subject to involuntary hospitalisation and treatment, after which pleural drainage follows local standards.

In these cases, the collection of data and follow-up will continue, and the participant will remain in the intention-to-treat population.

In participants allocated to the 'no pleural drainage' control group, pleural drainage may be used as an escape treatment (figure 1), if this is considered highly indicated by treating physician and the patient fulfils one or more of the following escape criteria:

- Suspected or confirmed haemothorax (e.g., due to recent thoracic trauma or intrathoracic surgery).
- Suspected or confirmed pneumothorax (e.g., by anamnesis or by clinical presentation, e.g., due to presence of subcutaneous emphysema, or on radiographic or ultrasonographic assessment,).

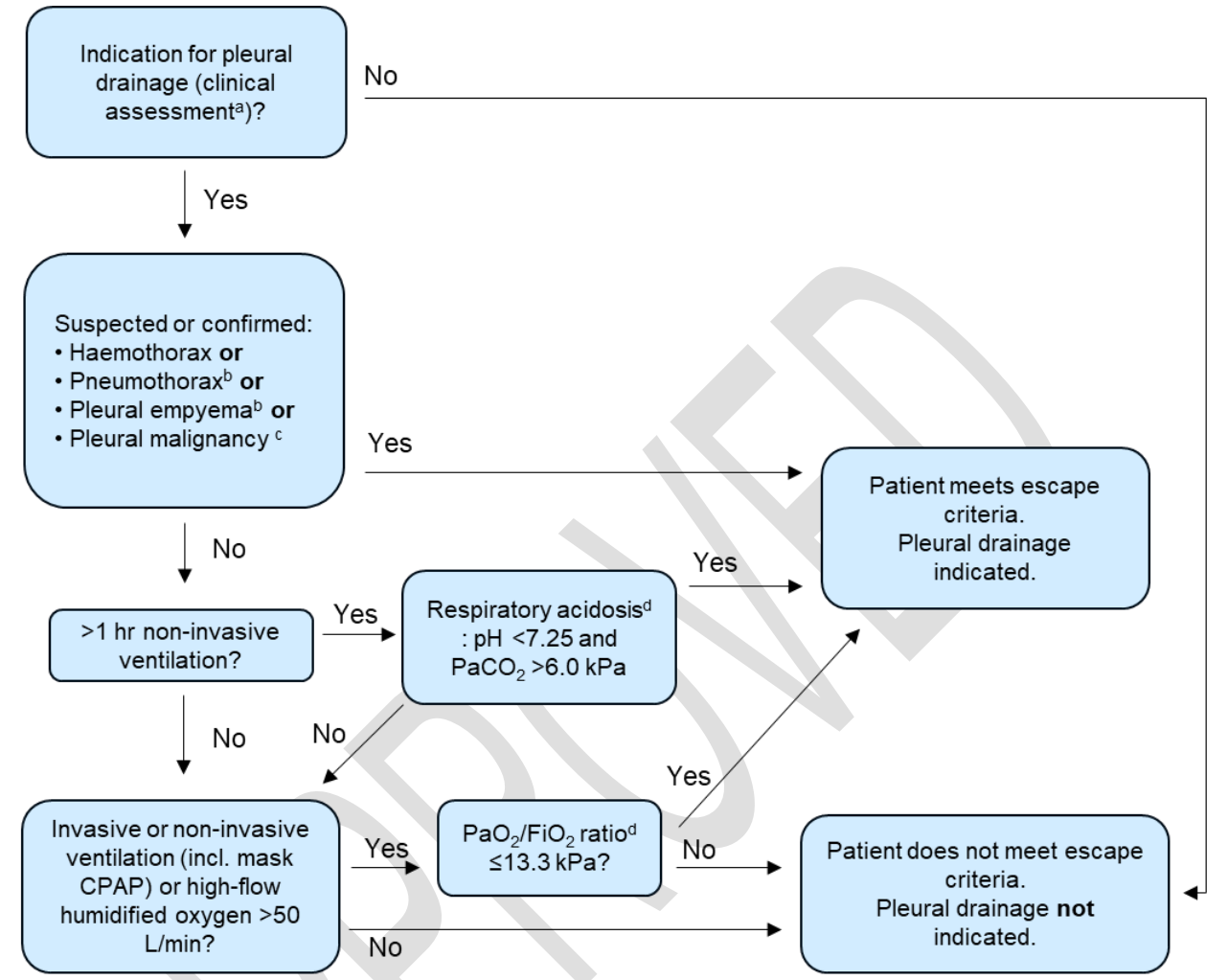
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- Suspected or confirmed pleural empyema (e.g., by anamnesis or clinical presentation, or on CT, MRI or ultrasonographic assessment).
- Pleural malignancy (suspected or confirmed pleural lymphoma, pleural metastases or direct pleural invasion, or malignant mesothelioma).
- Receives invasive or non-invasive mechanical ventilation or mask CPAP with PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis at the time of decision to conduct pleural drainage.
- Receives high-flow humidified oxygen therapy with a flow ≥ 50 L/min and a PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis at the time of decision to conduct pleural drainage.
- Have a respiratory acidosis with a pH < 7.25 and a $PaCO_2$ > 6.0 kPa in the most recent ABG analysis in spite of non-invasive ventilation for > 1 hour, at the time of decision to conduct pleural drainage.

In these cases, if a pleural drain is inserted, the participant remains in the trial and additional pleural drain insertions within 90 days from randomisation follow the allocated strategy of no drainage. The participant will remain in the intention-to-treat population.

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Figure 1



[a] by treating physician.
[b] by anamnesis or clinical presentation or on CT, MRI or ultrasonographic assessment. E.g. presence subcutaneous emphysema in pneumothorax.
[c] e.g. pleural lymphoma, malignant mesothelioma, pleural metastases or direct pleural invasion.
[d] on most recent arterial blood gas analysis.
CPAP: continuous positive airway pressure, CT: computed tomography, MRI: magnetic resonance imaging, $PaCO_2$: arterial partial pressure of carbon dioxide, PaO_2/FiO_2 ratio: arterial partial pressure of oxygen to fraction of inspired oxygen.

If an ineligible patient is randomised by mistake, i.e., patients who retrospectively are found not to have complied with one or more inclusion or exclusion criteria, the patient will continue in the trial and in the intention-to-treat population but may deviate from the allocated strategy as by the criteria defined above.[25]

We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide. Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment.

Participants who are discharged to another ICU will be regarded as discharged from the ICU unless the receiving ICU is an active DOPE-ICU feasibility trial site. If so, the participant will continue the allocated intervention at the new trial site until discharge from the ICU. Participants referred to intermediate or step-up/step-down beds cared for by ICU staff trained in the DOPE-ICU feasibility trial protocol will continue the allocated intervention and are still considered admitted to the ICU. Patients transferred to a non-participating ICU will be followed up for all outcome measures.

5. Selection and trial sites and personnel

5.1 Trial sites and setting

Trial sites will be ICUs in Denmark. Only ICUs with bedside ultrasonography available to staff physicians will be accepted as trial sites.

5.2 Trial personnel

All doctors caring for patients in participating ICUs will be eligible to enrol patients in the trial and all hospital doctors competent in conducting ultrasonography-guided pleural drainage as by local standards will be eligible to perform the interventions in trial participants. All clinicians caring for patients will be eligible to care for trial participants. All participating ICUs and doctors performing ultrasonography-guided pleural drainage in ICU patients, e.g., from the department of clinical radiology, will receive written and oral instructions about trial procedures. A 24-hour hotline will be available for trial-related questions.

6. Trial interventions

6.1 Experimental intervention

Ultrasonography-guided pleural drainage with insertion of a small-bore intrapleural catheter (typically pig-tail type catheter, size 6-14 French), typically conducted by intensivists or radiologists, as by local standards, of the pleural cavity with the estimated largest pleural effusion is conducted as soon as possible and is connected to a closed pleural drainage system

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as by local standards. A time interval of up to 24 hours from randomisation to intervention is expected to plan pleural drainage by a competent physician, and to allow for reversal of antithrombotic treatment or coagulation deficiency as by local recommendations and standards. If bilateral pleural effusions ≥ 2 cm are present at randomisation, drainage of contralateral pleura should be conducted as soon as possible according to local standards, at least within 24 hours from insertion of the first pleural catheter unless pleural effusion has receded to < 2 cm prior to drainage. Inserted pleural catheters remain in situ and open until removed at clinicians' discretion according to local standards.

If a new pleural effusion ≥ 2 cm is detected at any time during ICU stay within 90 days from randomisation, including during ICU readmissions, either contralaterally or ipsilaterally after pleural catheter removal, additional pleural drain insertion should be conducted following the procedure described above.

6.2 Control intervention

No pleural drainage is conducted during ICU stay, including readmissions, in 90 days from randomisation, unless escape protocol criteria is present (see section *4.3.2 Discontinuation and withdrawal at the choice of the investigator*).

6.3 Co-interventions

All patients in the trial will be given co-interventions as decided by the clinicians as ICU treatment and management in general will be at the discretion of the treating clinicians in all other aspects than pleural drainage.

6.4 Concomitant interventions

All other interventions are allowed. The use of concomitant interventions for respiratory failure should be based on updated international guidelines.[26–30] Particularly, we suggest the following to trial sites:

- Heated humidified high-flow nasal oxygen supplementation as the primary non-invasive treatment modality for hypoxic respiratory failure[30].
- Non-invasive ventilation as the primary non-invasive treatment modality for hypercapnic respiratory failure[29].

- Invasive mechanical ventilation being supplied as lung protective ventilation with tidal volumes of 4-8 ml/kg predicted body weight and plateau pressure of < 30 cm in acute respiratory distress syndrome (ARDS)[26,28].
- Use of prone positioning for > 12 hours/day in severe ARDS[26,28].

6.5 Criteria for modification of interventions for a given trial participant

The clinical team may at any time violate the protocol if they find it to be in the best interest of the participant. We will have a 24-hour DOPE-ICU feasibility trial hotline to enable discussion around the clock between the clinicians caring for trial participants and the DOPE-ICU feasibility trial team regarding protocol related issues.

6.6 Assessment of protocol compliance

Protocol violations will be monitored and defined according to following criteria:

- Participants allocated to pleural drainage who do not receive this within 24 hours from randomisation.
- Participants allocated to pleural drainage with bilateral pleural effusion who do not receive the second (contralateral) pleural drainage within 24 hours from the primary drainage, unless pleural effusion has receded < 2 cm.
- Participants allocated to no pleural drainage who receive pleural drainage at any time during ICU stay within 90 days from randomisation, including ICU readmissions, except when escape criteria for pleural drainage are present as specified (see section *4.3.2 Discontinuation and withdrawal at the choice of the investigator*). Pleural drainage according to escape criteria will be registered but will not represent a protocol violation.

7. Outcomes

7.1 Primary outcome (feasibility)

Proportion of patients receiving pleural drainage during ICU stay, within 90 days from randomisation.

7.2 Secondary outcomes

7.2.1 Secondary feasibility outcomes

- Proportion of patients with one or more protocol violations as defined under “6.6. Assessment of protocol compliance”.
- Proportion of included patients out of the number of eligible patients, i.e., patients who comply with all inclusion and exclusion criteria, in the inclusion period.
- Proportion of randomised patients with consent withdrawn for use of data.

7.2.2 Secondary clinical outcomes

- All-cause mortality within day 90 from randomisation.
- Proportion of patients with one or more serious adverse events (SAEs) within 90 days after randomisation; SAEs are defined as new pneumothorax requiring invasive treatment (drainage or surgery), new haemothorax requiring red blood cell transfusion, new blood stream infection defined as any cultured microorganism from any blood sample except microorganisms clearly specified to be contaminants or likely contaminants by the microbiological department, and new episode of invasive mechanical ventilation defined as endotracheal intubation or re-intubation after extubation or tracheal decannulation.
- Absolute number of days alive without life support being the use of mechanical ventilation, renal replacement therapy, or circulatory support in the 90-day period.
- Absolute number of days alive and out of hospital in the 90-day period.

Several of the outcomes above are composite outcomes. The single components of these will also be analysed and presented in the final publication.

7.2.3 Secondary process outcomes

- Proportion of patients with new pleural infection after 24 hours from randomisation defined as any positive pleural fluid culture of any fungi or bacteria except coagulase-negative Staphylococci, Enterococci, and Corynebacterium species, which will be considered contaminants, in any pleural fluid sampling conducted within the 90-day follow-up period.
- PaO_2/FiO_2 ratio in the ABG analysis conducted in ICU closest to 24 and 72 hours after randomisation.

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- pH in the ABG analysis conducted in ICU closest 24 and 72 hours after randomisation.
- $PaCO_2$ in the ABG analysis conducted in ICU closest to 24 and 72 hours after randomisation.

In patients diseased or discharged from the ICU within 24 to 72 hours, the last available ABG analyses in the ICU will be used. For patients diseased or discharged within 24 hours, this means that the same values will be used for both the 24 and 72 hours registrations.

Differences (∆) of ABG parameters from individual baseline registrations will be reported supplementally.

Substudies will be encouraged as long as they do not hamper the completion of the main protocol and can be conducted after approval of the protocol by the Steering Committee. Specific protocols will be sent for approval before they will be included as part of the main study.

8. Safety

8.1 Definitions

In the DOPE-ICU feasibility trial we will use the definitions bellow.[24]

Adverse event (AE): any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Serious adverse event (SAE): any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

8.2 Risk and safety issues in the current trial

The trial participants will all be ICU patients for whom all adverse events and reactions are documented routinely in the patient health record (i.e., ICU notes, charges, and laboratory reports).

We will record in the eCRF the occurrence of SAEs in the full 90-day period for all included patients and report SAEs as outcomes measures.

Ultrasonography-guided pleural drainage with insertion of a small-bore intrapleural catheter is a common intervention in the ICU, and the participants in this trial will not have a significantly

different risk profile than other ICU patients. Known adverse events to pleural drainage include pneumothorax, haemothorax and pleural infection, the frequency of these however is very low, with pneumothorax as the most common adverse event having an incidence of 0.8% or even lower with procedural ultrasonographical guidance.[17,18] The patients will be in ICU and closely monitored by clinical staff who can intervene at any time. In case of progressing respiratory failure, specific escape criteria for conducting pleural drainage in patients allocated to the 'no pleural drainage' control group are defined to avoid harm from the non-interventional approach (see section *4.3.2 Discontinuation and withdrawal at the choice of the investigator*).

8.3 Assessment of adverse events

8.3.1 Timing

SAEs will be registered in the eCRF daily during ICU admission where the risk of these events is considered the highest. Any SAEs occurring after discharge from the ICU will be captured in the eCRF in the 90-day follow-up form.

8.3.2 Classification of an event

The following are considered SAEs in the DOPE-ICU feasibility trial with definitions as in the secondary SAE outcome:

- New pneumothorax
- New haemothorax
- New blood stream infection
- New episode of invasive mechanical ventilation

When ipsilateral post-drainage (or drainage attempt) pneumothorax or haemothorax is registered in the eCRF in the intervention arm of the DOPE-ICU feasibility trial, the sponsor (or delegated party) will be notified and will assess the events individually to assess potential causality between the SAE and the intervention. Cumulated SAE proportions for both the intervention group and the control group will be included in the yearly safety reports, together with causality assessments.

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8.4 Reporting

Any SAE not covered in the secondary outcomes (defined in 7.2) adjudicated to be related to the trial intervention by the investigator, will be reported within 24 hours to the Sponsor (or delegated party). If the SAE is assessed as being related to the trial intervention by Sponsor, and are life-threatening or fatal, no later than 8 days after the reporting, the Sponsor will inform the relevant Ethics Committee of relevant information on the Sponsor's and the investigator's follow-up action to the life-threatening or fatal SAE.

9. Procedures, assessments and data collection

9.1 Inclusion procedure

Routine daily ultrasonographic examinations of pleurae in patients with respiratory failure will be encouraged in all participating sites to identify patients fulfilling the inclusion criteria.

9.1.1 Screening

All patients admitted to a participating ICU and fulfilling all inclusion criteria will be screened in the REDCap® eCRF by physicians, medical students or trial personnel working under the responsibility of a trained physician.

9.1.2 Procedures for informed consent

The trial is an acute trial in temporarily incompetent patients, who will be enrolled when eligible. As soon as possible after enrolment, informed consent will be obtained from the patient's next of kin and a physician, who is independent of the trial (trial guardian). Participants, who regain competence, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial, so he/she is able to make an informed decision about participation in the trial.

The information will be given in a separate room, and the consenting party has the right to bring a companion. Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

Collection of informed consent will be performed by all trial personnel (study nurses, medical students, physicians). If questions arise during the consent process responsible study personnel can be reached through a 24-hour hotline. All personnel with functions related to obtainment of

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informed consent in the DOPE-ICU feasibility trial will be trained and approved before engaging in the trial.

Trial guardian: After enrolment in the trial, written consent from the trial guardian must be obtained as soon as possible. If the trial guardian does not consent, the patient will be withdrawn from the trial and management of pleural effusions and pleural drainage will follow local standards at the discretion of the treating clinicians. All attempts of collecting the written consent must be documented in the medical chart or in a log.

Next of kin: After enrolment in the trial consent from the next of kin must be obtained as soon as possible. The consent can initially be oral, obtained over the phone, if the next of kin cannot be physically present at the hospital. If so, the next of kin's full name, date and time of consent will be written in the medical chart. Written informed consent must be obtained as soon as possible.
Information should always be adjusted to the situation. Oral and written information about the trial must be provided. The relatives must have time to read the material, think about it and ask questions about the trial before they give their written consent.
If the next of kin do not consent, the patient will be withdrawn from the trial and management of pleural effusions and pleural drainage will follow local standards at the discretion of the treating clinicians. The next of kin will be asked permission to continue data collection after withdrawal. Specifically, the next of kin will be asked for permission to continue registration of the data from the patient's electronic journal and medical charts for the purpose of obtaining as complete a trial dataset as possible, which is important for the final interpretation of the trial results. Only the specific data relevant for the trial up until 90-day follow-up will be registered, and it will be stressed to the next of kin, that continued data collection or the decision to accept this or not, does not affect the treatment the patient receives. If the next of kin consents to continued data registration, a separate written consent for this will be obtained. All contacts to the next of kin concerning the consent must be documented in the patient files, log or similar.

The patient: When the patient regains competence, he/she will receive written and oral information about the trial. If a competent patient has difficulties in reading and writing because of acute/chronic disease a witness can be used to document the patient's consent. The witness can be a nurse or other. The witness must write his/hers name in capital letters, signature, date and that they witness the patient's consent. Most patients are regarded competent when their

treatment in the ICU is ended and they are referred to another department. If the patient is under legal guardianship, the guardian will be the consent provider on behalf of the patient. If informed consent has not been obtained at discharge from the hospital, the patient must be contacted by phone and the written information about the trial and consent form mailed or send by post. If a patient at the time of referral to another department or home is not competent because of brain injury, delirium, psychosis, or other conditions. Informed consent must be obtained later. The patients must regularly be contacted and re-evaluated for re-regained competence. All contacts must be documented in a file or log. If the patient remains incompetent at 90 days after inclusion, further attempts of consent obtainment ceases.

If the patient does not consent, the patient will be withdrawn from the trial and management of pleural effusions and pleural drainage in the ICU will follow local standards at the discretion of the treating clinicians. The patient will be asked permission to continue data collection after withdrawal. Specifically, the patient will be asked for permission to continue registration of the data from his/her electronic journal and medical charts for the purpose of obtaining as complete a trial dataset as possible, which is important for the final interpretation of the trial results. Only the specific data relevant for the trial up until 90-day follow-up will be registered, and it will be stressed to the patient, that continued data collection or the decision to accept this or not does not affect the treatment the patient receives. If the patient consents to continued data registration, a separate written consent for this will be obtained.

Lack of informed consent from the patient, and the patient dies: If the patient dies before informed consent from the patient has been obtained and consent by the trial guardian or the patient's next of kin is obtained either written or orally and documented in patient files, log or similar, collected data will be kept for analysis.

Deviation from the standard informed consent: According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

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9.2 Data collection

9.2.1 Method

Data will be collected and managed in the trial eCRF using REDCap®. Data will be obtained from the patients' hospital files and national/regional/hospital registers (source data as defined per site and region). For patients transferred from a trial ICU to a non-trial ICU, data related to the outcomes of interest will be collected after transfer e.g., through the central Danish health portal (Sundhed.dk) after obtained approval from the Danish Health Data Authority as required, through regional electronic patient journals, phone calls, e-mail correspondence and/or patient charts.

9.2.2 Timing

The following variables will be obtained at the specified time points.

At screening:

- Patient identification number
- Inclusion criteria:
  - Acute admission to the ICU (yes/no)
  - Age (years)
  - Estimated pleural effusions right and left side (cm)
  - Type of respiratory support: Invasive ventilation, non-invasive ventilation, or oxygen on open systems
  - pH (decimal)
  - $PaCO_2$ (kPa)
  - Expected ICU stay > 24 hours
- Exclusion criteria:
  - Mediastinal or pleural drains in situ (yes/no)
  - Suspected or confirmed haemothorax (yes/no)
  - Suspected or confirmed pneumothorax (yes/no)
  - Suspected or confirmed pleural empyema (yes/no)
  - Pleural malignancy (yes/no)
  - Clinically assessed absolute indication for pleural drainage and:
    - Invasive or non-invasive mechanical ventilation or mask CPAP with PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis.

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    - High-flow humidified oxygen therapy with a flow ≥ 50 L/min and a PaO_2/FiO_2 ratio ≤ 13.3 kPa in the most recent ABG analysis.
    - Persistent respiratory acidosis with a pH < 7.25 and a $PaCO_2$ > 6.0 kPa in the most recent ABG analysis in spite of non-invasive ventilation for > 1 hour.
  - Antithrombotic treatment or coagulation deficiency incompatible with pleural drainage and contraindications to reversal of this (yes/no)
  - Withdrawal from active treatment or brain death deemed imminent (yes/no)
  - Pregnancy (yes/no)
  - Under coercive measures (yes/no)
  - Consent obtained (yes/unobtainable)
- Name
- Trial site

Baseline:

- Date of admission to hospital (ddmmyyyy)
- Date (ddmmyyyy) and time (hh:mm) of admission to ICU
- Pre-ICU location (emergency department or pre-hospital setting/general ward/operating or recovery room/different ICU)
- Elective surgery during current hospitalization (yes/no)
- Height (cm)
- Weight (kg)
- If invasively mechanically ventilated: FiO_2 (fraction) at the time of the last ABG prior to randomisation, Peak pressure, tidal volume, positive end-expiratory pressure (cm H_2O), positioning of the patient (supine/prone)
- If non-invasively ventilated: FiO_2 (fraction) at the time of the last ABG prior to randomisation, end-expiratory pressure (cm H_2O)
- If open systems, type (nasal cannula/mask/non-rebreather mask), flow (L/min) and fraction (decimal) of oxygen supplementation at the time of the last ABG prior to randomisation
- PaO_2 in last ABG prior to randomisation (kPa)
- SaO_2 in last ABG prior to randomisation (%)
- Highest p-lactate in 24 hours prior to randomisation
- Acute illness:

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  - Pneumonia (right-sided/left-side/bilaterally/none)
  - Multiple trauma (yes/no)
  - Myocardial infarction (yes/no)
  - Resuscitated from cardiac arrest (yes/no)
  - ARDS (yes/no)
  - Sepsis (yes/no), if yes, suspected or confirmed site/sites of infection (pulmonary/abdominal/urinary or genital/central nervous system/soft tissue/intravascular/unknown)
- Simplified Mortality Score for the Intensive Care Unit (SMS-ICU) [31]
  - Lowest systolic arterial pressure in 24 hours prior to randomisation
  - Use of inotropes within 24 hours prior to randomisation (yes/no)
  - Use of continuous infusion of vasopressors within 24 hours prior to randomisation (yes/no), if yes, highest dose of dopamine, norepinephrine and adrenaline (µg/kg/min)
  - Use of renal replacement therapy (yes/no)
- Comorbidities:
  - History of ischaemic heart disease (yes/no)
  - Chronic heart failure (yes/no)
  - Active metastatic cancer (yes/no)
  - Active haematological malignancy (yes/no)
  - Chronic obstructive pulmonary disease (yes/no)
  - Chronic dialysis (yes/no)

Daily during ICU stay:

- Pleural drainage conducted (yes/no), if yes, side (left/right) and time (hh:mm) of drainage, conducted by (radiologist/intensivist/surgeon/other (describe)).
  - If yes, indication for pleural drainage (pleural effusion ≥ 2 cm (in intervention group); haemothorax; pneumothorax; pleural infection; pleural malignancy; invasive or non-invasive ventilation and PaO_2/FiO_2 ratio ≤ 13.3 kPa; high-flow oxygen therapy with flow ≥ 50 L/min and PaO_2/FiO_2 ratio ≤ 13.3 kPa; respiratory acidosis despite non-invasive ventilation for > 1 hour; other (describe)).
- Pleural catheter in situ including catheters inserted or removed on this day (yes/no), if yes, side (left/right) with fluid output (mL) and pleural catheter removed (yes/no), if yes, time (hh:mm) of removal

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- PaO_2 and arterial oxygen saturation (%) in the ABG conducted closest to 20:00 with concomitant FiO_2 (fraction) in closed systems or flow (L/min) and oxygen fraction in open systems
- Highest $PaCO_2$ with concomitant pH
- Serious adverse events:
  - Pneumothorax (yes/no)
  - Haemothorax (yes/no)
  - Mechanical ventilation on this day (yes/no), if yes, patient proned on this day (yes/no), ventilator settings closest to 20:00 (tidal volume/positive end-expiratory pressure/peak pressure) and type of ventilation (invasive/non-invasive or CPAP), if invasive, were the patient intubated or re-cannulated on this day (yes/no)
- Infusion of vasopressors or inotropes (yes/no)
- Renal replacement therapy (yes/no)
- Cumulated dose of furosemide on this day
- Cumulated dose of thiazides on this day
- Cumulated dose of spironolactone on this day

On Day 2 and 4 (specifically):

- PaO_2 with concomitant arterial oxygen saturation (%) and FiO_2 (fraction) in closed systems or flow (L/min) and oxygen fraction in open systems in the ABG analysis conducted in ICU closest to 24 and 72 hours after randomisation.
- $PaCO_2$ in the ABG analysis conducted in ICU closest to 24 and 72 hours after randomisation.
- pH in the ABG analysis conducted in ICU closest to 24 and 72 hours after randomisation.

On ICU discharge:

- Date and time of discharge
- Where were the patient discharged to
- Readmission time (hh:mm) and date (ddmmyyyy)

Withdrawal:

- Date (ddmmyyyy) and time (hh:mm) of withdrawal
- Who is not giving consent or withdrawing consent (trial guardian/next of kin/patient)
- Permission to continue data registration (yes/no)

90-day follow-up:

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- Date of 90-day follow-up (ddmmyyyy)
- Pneumothorax outside the ICU (yes/no), if yes, side (left/right) and date of occurrence (ddmmyyyy)
- Haemothorax outside the ICU (yes/no), if yes, side (left/right) and date of occurrence (ddmmyyyy)
- Blood stream infection in the 90-day period if yes, type of microorganism cultured and date of occurrence (ddmmyyyy)
- Pleural fluid sampling for culturing conducted in the 90-day period (yes/no), if yes, positive result in any culture (yes/no)), if yes, type of bacteria or fungus and date and time of pleural fluid sampling conducted (ddmmyyyy)
- Pleural drainage outside participating ICU in the 90-day period
- Reintubated or re-cannulated in non-participating ICU (yes/no)
- Days with mechanical ventilation, dialysis, and vasopressors in non-participating ICU.
- Discharge from hospital (yes/no), if yes, date (ddmmyyyy) and readmission (yes/no), if yes, dates of readmissions (ddmmyyyy-ddmmyyyy)
- Death within 90 days (yes/no), if yes, date of death (ddmmyyyy)

10. Data handling and record keeping

10.1 Data management

Data will be collected and managed in the trial eCRF using the REDCap® electronic data capture tools hosted In the North Denmark Region. REDCap® is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.[23,32]

The coordinating investigator, principal investigator, or principal investigator's delegate will construct and oversee the REDCap® eCRF. The randomisation list will be generated in the REDCap® system, concealed from all investigators, including the coordinating and principal investigators. Investigators from all participating sites will have access to enter data into the eCRF. Only the coordinating and principal investigators will be able to export data from the trial database.

10.2 Confidentiality

Each participant will receive a unique trial identification number. Trial investigators will receive a personal username and password to access the randomisation system and the eCRF. Each site will only have access to site specific participant data. Data will be handled according to the National Data Protection Agency and protected by the Danish national laws 'Loven om behandling af personoplysninger' and 'Sundhedsloven'.

10.3 Biobanking

No biobank will be formed.

10.4 Access to data

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived for 15 years. De-identified data may be made publicly available after the publication of the outcome data.

11. Statistical plan and data analysis

11.1 Sample size and power

11.1.1 Sample size estimation

A total of 88 patients will be needed to detect or reject an expected 75% relative increase (an absolute increase of 30 %-points) in patients receiving pleural drainage in the intervention group, assuming a maximal incidence of pleural drainage in the ICU within 90 days of 40% in the control group, with a type 1 error risk (two-sided α) of 0.05 and a type 2 error risk (β) of 0.20 (power of 80%), and an added 4 patients due to an expected dropout rate of maximum 5%.

11.1.1 Power estimations for secondary outcomes

The trial is only powered to show relevant differences on the primary feasibility outcome of proportions of patients receiving pleural drainage in the ICU within 90 days. Therefore, results in all other outcomes should be considered explorative only. Nevertheless, results in the secondary clinical outcomes may guide sample size estimations and simulations for the subsequent main DOPE-ICU trial.

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11.2 Statistical methods

All analyses will be conducted in the intention-to-treat population being all randomised patients except those where outcome data cannot be obtained due to withdrawal of consent.[24,33,34]

The primary outcome (proportion of patients receiving pleural drainage in the ICU within 90 days) will be analysed using a generalised linear model with a log-link and Poisson data distribution according to the relation between variance and mean, and a robust variance estimation adjusted for the stratification variable site. Significance of the intervention will be assessed based on the p value from this regression and reported with the readily available risk ratio with 95% confidence interval. A similar analysis, however, with an identity-link and Poisson data distribution instead to produce the risk difference with 95% CI, will be conducted as well. Dichotomous secondary outcomes will be analysed similarly to the primary outcome, however, no p values will be reported given the lack of power and explorative nature of these outcomes. Continuous and ordinal secondary outcomes will be analysed using a generalised linear model with an identity-link, Gaussian data distribution and a robust variance estimation, adjusted for the stratification variable site to produce a mean difference with 95% CI. A generalised linear model will be applied, regardless of expected non-normal data distribution of the residuals. Similarly, to the other secondary outcomes, no p values will be reported.

For the secondary process outcomes, an additional analysis will be conducted similarly, investigating the difference (Δ) in the PaO_2/FiO_2 ratio, $PaCO_2$ and pH, respectively, between individual baseline and 72-hour measurements.

Additional per-protocol sensitivity analyses will be conducted for all secondary clinical and process outcomes, excluding patients with one or more protocol violations.

11.2.1 Significance

A two-sided P value (α) < 0.05 will be considered statistically significant. The power to detect or reject a difference of 75% relative increase (an absolute increase of 30 %-points) in the primary outcome in the intervention group will be 80% (1-β) (see section 11.1.1 *Sample size estimation*).

11.2.2 Interim analysis

As this is a feasibility trial, no interim analyses will be conducted and similarly, no independent Data Monitoring and Safety Committee will be formed.

11.2.3 Early stopping criteria

As this is a feasibility trial, early stopping criteria are not applicable.

11.2.4 Accountability procedure for missing data/population for analysis

We will use an eCRF with a pragmatic design and incentive strategies to maximise complete registration in order to minimise the occurrence of missing data. If less than 5% of the data are missing on the primary outcome, a complete case analysis without input of missing values will be performed. If missing data are more than 5%, multiple imputation using chained equations will be performed by creating at least ten input data sets under the assumption that the data are missing at random.[35,36] We will use all outcomes and major prognostic baseline characteristics being size of estimated largest pleural effusion (in cm), location of pleural effusion ≥ 2 cm (right, left or bilaterally), age, active metastatic cancer, active haematological malignancy, chronic obstructive pulmonary disease, type of admission (medical, elective surgical or emergency surgical) and SMS-ICU score in the multiple imputation. If multiple imputation is used, then the primary result of the trial will be based on the imputed data. The unadjusted, non-imputed analysis will also be made available. If multiple imputation is used, we will use a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the “best-worst-case” scenario it is assumed that all patients lost to follow-up in the experimental group have received pleural drainage in the ICU within 90 days; and none of those with missing outcomes in the control group have received pleural drainage. Conversely, in the “worst-best-case” scenario, it is assumed that none of the patients who were lost to follow-up in the experimental group received pleural drainage in the ICU within 90 days; and that all those lost to follow-up in the control group received pleural drainage.

12. Quality control and quality assurance

The coordinating investigator will be responsible for organising the trial sites including education of local investigators, research nurses, and other trial site staff before the initiation of the trial. The education will be continuously documented, and an annual investigator meeting will be planned.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of patients and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial patients.

12.1 Monitoring the intervention groups

No external monitoring will be applied. A centralised day-to-day monitoring of the eCRF will be conducted by the coordinating investigator and his delegates.

13. Legal and organisational aspects

13.1 Finance

13.1.1 Trial funding

The DOPE-ICU feasibility trial is funded by “Læge Sofus Carl Emil Friis og Hustru Olga Doris Friis’ legat” [FID4401466] (650.000 DKr) and “Region Nordjyllands Sundhedsvidenskabelige Forskningsfond” [2024-0049] (90.000 DKr). The funding sources will have no influence on the trial design or conduct, data handling, analysis, or publication. Additional trial funding may be applied for through relevant public and possibly private funding agencies.

13.1.2 Compensation

No economic compensation will be given for trial sites. Trial sites will be granted co-authorship as stated in *13.3.1 Publication and authorship*.

13.2 Insurance

In Denmark, the Patient Insurance Association insures all trial participants.

13.3 Plan for publication, authorship and dissemination

13.3.1 Publication and authorship

The trial will be registered on ClinicalTrials.gov prior to initiation. The final protocol will be published as a design and rationale paper including the detailed plan for analyses. Upon trial completion the main manuscript with trial results whether positive, negative or neutral will be submitted for peer-reviewed publication in a relevant international journal, preferably open access. Funding sources will have no influence on the writing of the manuscript or the decision to publish.

All Steering Committee members will gain authorship, Marie S. Worm will be the first author and Olav L. Schjørring the last. Site investigators will gain authorship at the site’s first randomisation. For each 10 included patients, the site will receive an additional authorship. Fulfilling Vancouver definitions for authorship is a prerequisite.

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13.4 Spin-off projects (if any)

Spin-off projects will be encouraged and conducted when approved by the Steering Committee. Presently no spin-off projects have been developed.

13.5 Intellectual property rights

The sponsor and primary investigator is OL Schjørring. Therefore, no control of intellectual property rights is needed. The initiative for the DOPE-ICU trial has been taken by OL Schjørring and BS Rasmussen and supplemented by doctors at multiple ICUs, none of whom have affiliations to institutions that may have economic interests in the trial results. Contracts between site investigators and Sponsor will be signed before site initiation.

13.6 Organisational framework

The trial will be conducted in collaboration with national and international partners in the Collaboration for Research in Intensive Care (CRIC) network (https://www.cric.nu/).

13.7 Trial timeline

2023 – November 2024: Governance approval applications, education of trials sites, other preparations.
November 2024: First patient enrolled.
July 2025: Last patient enrolled.
October 2025: Follow-up completed.

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