RESEARCH PROTOCOL

Personalized Mechanical Ventilation Guided by UltraSound in Patients with Acute Respiratory Distress Syndrome (PEGASUS)

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LIST OF ABBREVIATIONS

AMC	Academisch Medisch Centrum
APACHE	Mortality prediction scores in ICU patients
ARDS	Acute Respiratory Distress Syndrome
AVG	Algemene Verordening Gegevensbescherming
CCMO	Centrale Commissie Mensgebonden Onderzoek
CT	Computertomografie
CXR	Chest X-ray
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GAMLSS	Generalized Additive Model for Location, Scale and Shape
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
HFNO	High Flow Nasal Oxygen
ICU	Intensive Care Unit, patientcare under supervision of an intensivist
IQR	InterQuartile Range
IRB	Institutional Review Board
LUS	Lung UltraSound
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
$PaCO_2$	Partial Pressure of Carbondioxide
PaO_2	Partial Pressure of Oxygen
PBW	Predicted Body Weight
PEEP	Positive End-Expiratory Pressure
PPeak	Peak Pressure
PPLAT	Plateau Pressure
PS	Pressure Support
PSV	Pressure Support Ventilation
RASS	Richmond Agitation and Sedation Scale, a validated and reliable method to assess patients' level of sedation in the ICU

RCT Randomized Clinical Trial

RR Respiration Rate

SAE Serious Adverse Event

SaO_2 Arterial Saturation of Oxygen

SD Standard Deviation

SOFA Sequential Organ Failure Assessment, score to determine level of organ dysfunction and mortality risk in ICU patients.

Sponsor The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.

UMC Universitair Medisch Centrum

VFD Ventilator Free Days, when a patient is on a ventilator for less than 1 hour per 24 hours.

ECMO Extracorporeal Membrane Oxygenation

WGBO Wet op de Geneeskundige Behandel Overeenkomst

WMO Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale

Acute respiratory distress syndrome (ARDS) is a frequent cause of hypoxemic respiratory failure with a mortality rate of approximately 30%. The identification of ARDS phenotypes, based on focal or non-focal lung morphology, can be helpful to better target mechanical ventilation strategies of individual patients. Lung ultrasound (LUS) is a non-invasive tool that can accurately distinguish ‘focal’ from ‘non-focal’ lung morphology. We hypothesize that LUS-guided personalized mechanical ventilation in ARDS patients will lead to a reduction in 90-day mortality compared to conventional mechanical ventilation.

Objective

The aim of this study is to determine if personalized mechanical ventilation based on lung morphology assessed by LUS leads to a reduced mortality compared to conventional mechanical ventilation in ARDS patients.

Study design

The PEGASUS study is an investigator-initiated multicenter randomized clinical trial (RCT) with a predefined feasibility and safety evaluation after a pilot phase.

Study population

This study will include 538 consecutively admitted invasively ventilated adult intensive care unit (ICU) patients with moderate or severe ARDS. There will be a predefined feasibility and safety evaluation after inclusion of the first 80 patients.

Intervention

Patients will receive a LUS exam within 12 hours after diagnosis of ARDS to classify lung morphology as focal or non-focal ARDS. Immediately after the LUS exam patients will be randomly assigned to the intervention group, with personalized mechanical ventilation, or the control group, in which patients will receive standard care.

Main study parameters/endpoints

The primary endpoint is all cause mortality at day 90 (diagnosis of ARDS considered as day 0). Secondary outcomes are mortality at 28 days, ventilator free days (VFD) at day 28, ICU length of stay, ICU mortality, hospital length of stay, hospital mortality and number of complications (VAP, pneumothorax and need for rescue therapy). After a pilot phase, feasibility of LUS, correct interpretation of LUS images and correct application of the intervention within the safe limits of mechanical ventilation is evaluated to inform a stop-go decision.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Patient burden and risks are low as the ventilation methods in this study are already commonly used in ICU practice; the collection of general data from hospital charts and (electronic) medical records systems causes no harm to the patients; LUS is not uncomfortable.

1 INTRODUCTION AND RATIONALE

1.1 Heterogeneity in ARDS

Acute respiratory distress syndrome (ARDS) is a frequent cause of hypoxemic respiratory failure and is characterized by protein rich pulmonary edema[1]. Around one-in-four invasively ventilated patients in the intensive care unit (ICU) develops ARDS and it has a high hospital mortality rate of approximately 30%[2]. Diagnosis is based on a set of clinical and radiological criteria[3,4], resulting in a remarkable and unacceptable physiological, radiological and biological heterogeneity[5,6,7]. The notion that there is no 'typical' ARDS may be the reason why many clinical trials failed to demonstrate benefit of interventions, that were almost exclusively provided to an unselected group of ARDS patients[1].

1.2 ARDS phenotypes based on lung morphology

The identification of ARDS phenotypes can be helpful to better target treatment of individual patients with ARDS[6]. Lung imaging with computed tomography (CT) revealed two distinct phenotypes of ARDS based on lung morphology. Lungs with diffuse and patchy loss of aeration (the 'non-focal' phenotype) generally respond well to recruitment while lungs with predominant dorsal-inferior consolidations (the 'focal' phenotype) respond better to prone positioning[8]. But differentiating these phenotypes using conventional chest radiography is challenging, leading to treatment that is often misaligned to the true lung morphology.

In the largest study to date testing a personalized ventilation strategy based on lung morphology, 20% of patients were misclassified, with poor interobserver agreement in the interpretation of chest images[9]. Even though there was no overall mortality benefit in all patients (classified correctly and incorrectly), patients with correctly classified lung morphology did benefit from a personalized ventilation strategy with a 10% decrease in mortality, while patients who were misclassified had a substantial increase in mortality when exposed to a misaligned personalized ventilation strategy[9]. Thus, accurate classification seems mandatory before starting a personalized ventilation strategy based on morphology.

1.3 Challenges in assessment of lung morphology

In daily clinical practice, the use of CT-scan in ARDS patients is severely limited since transport of critically ill patients to the scanner is often undesirable and comes with additional risks. Moreover, interpretation of CT-images can be complex, and should be performed by experienced physicians[9]. Chest radiography (CXR) is commonly performed in the ICU but the technique lacks good diagnostic accuracy for pulmonary pathologies in critically ill patients in general[10,11,12]. The accuracy is likely even worse for lung morphology as it gives a one-directional assessment of a phenotype that is defined by three-dimensional abnormalities. An alternative for lung imaging in critically ill invasively ventilated patients is highly needed[9].

Lung ultrasound (LUS) is gaining popularity in the ICU setting, because it can adequately assess lung aeration compared to CT and it is readily available at the bedside[13]. Moreover, LUS is easy to learn and it knows a very high interobserver agreement[13,14,15,16].

1.4 Current evidence on LUS in ARDS patients

Recently, our group developed a LUS method for classification of lung morphology in ARDS patients[17]. The method was trained and validated using multicenter international datasets of simultaneously acquired LUS and CT exams. The LUS method could correctly distinguish ‘focal’ from ‘non-focal’ lung morphology with a sensitivity of 77%, a specificity of 100% and an accuracy of 89% when compared to the gold standard chest CT, and thus could play an important role in in guiding personalized ventilation in ARDS patients.

1.5 Need for an RCT on LUS-guided personalized ventilation

In current clinical practice, ARDS patients are ventilated using lung-protective strategies, consisting of a low tidal volume and high positive end-expiratory pressure (PEEP), but not accounting for phenotypes within the ARDS population (see Table 1: standard of care)[18,19]. Personalized invasive ventilation based on lung morphology has great potential to reduce the high mortality in ARDS but only if classification of lung morphology is performed correctly[9]. LUS might be the ideal technique to satisfy the strong need for a reliable and widely available method to provide a more personalized invasive ventilation strategy. A randomized clinical trial (RCT) that will provide high

level of evidence for benefit of LUS–guided personalized ventilation is highly needed in daily ICU practice.

1.6 The PEGASUS study

The PEGASUS study is an investigator-initiated multicenter RCT. The objective of the study is to determine if personalized mechanical ventilation based on lung morphology assessed by LUS leads to a reduced mortality compared to conventional mechanical ventilation in ARDS patients.

1.7 Feasibility and safety

Given the above-described problems with patient classification in the LIVE study, it is pivotal to evaluate the feasibility and safety of personalized ventilation strategies during the inclusion in a RCT. Similar to the evaluation of a CXR, there could be misclassification based on a difference in interpretation of LUS images. The agreement between treating physician and an expert panel in the interpretation and the assessment of lung morphology therefore needs to be evaluated with a pilot phase to ensure that the intervention is delivered based on accurate classification. Furthermore, if the correct personalized strategy is indeed selected, it needs to be ensured that the intervention is delivered as intended and that this keeps within the “safe limits” of mechanical ventilation.

2 OBJECTIVES AND HYPOTHESIS

2.1 Primary objective

The primary objective of this study is to determine if personalized mechanical ventilation based on lung morphology assessed by LUS leads to a reduced all-cause mortality at day 90 (diagnosis of ARDS considered as day 0) compared to conventional mechanical ventilation in ARDS patients.

2.2 Secondary clinical objectives

The secondary objectives of this study are to determine if personalized mechanical ventilation based on lung morphology assessed by LUS leads to a reduced mortality at 28 days, more ventilator free days (VFD) at day 28, a shorter ICU length of stay, lower ICU mortality, shorter hospital length of stay, lower hospital mortality, lower number of patients with complications, and less need for adjunctive (ECMO, recruitment, prone position) and rescue therapies (Inhaled vasodilators, airway pressure release ventilation).

2.3 Objectives pilot phase of the study

The objective of the pilot phase is to ensure feasibility of the study, accurate application and interpretation of the LUS algorithm, and delivery of personalized mechanical ventilation within “safe limits”.

2.4 Primary hypothesis

Personalized mechanical ventilation based on lung morphology assessed by LUS reduces 90 days mortality in comparison to conventional mechanical ventilation in ARDS patients.

2.5 Secondary hypotheses

Personalized mechanical ventilation based on lung morphology assessed by LUS improves secondary outcomes of (1) effective and safe mechanical ventilation in terms of duration of mechanical ventilation and complications and (2) ICU and hospital length of stay.

3 STUDY DESIGN

This is an investigator-initiated, multicenter, superiority randomized clinical trial (RCT). The study will run in ±40 academic and non-academic centers (APPENDIX I).

This study includes a pilot phase to evaluate the feasibility of the personalized intervention.

4 STUDY POPULATION

4.1 Population (base)

We will recruit eligible consecutive patients with moderate or severe ARDS, according to the Berlin criteria, that are admitted to participating ICU's[3]. The ICU of the Amsterdam University Medical Centers (Amsterdam UMC) location Academic Medical Center (AMC) and approximately 40 other ICUs will include patients for this study. A total of 538 patients will be randomized, approximately 25 patients per center. Given that approximately 1 patient is expected to be recruited each 2 months, the recruitment period is approximately 2 years after all 40 sites started enrolling patients [20]. The planned pilot phase is restricted to the first 80 included patients.

4.2 Inclusion criteria

Patients will be included when they meet the following criteria:

1. admitted to a participating ICU,
2. invasively ventilated and
3. fulfil the Berlin criteria for moderate or severe ARDS (APPENDIX II).

4.3 Exclusion criteria

Patients will be excluded if they fulfil any of the following criteria:

1. age under 18,
2. participation in other interventional studies with conflicting endpoints,
3. conditions in which LUS is not feasible or possible (e.g. subcutaneous emphysema, morbid obesity or wounds),
4. mechanical ventilation for longer than 7 consecutive days in the past 30 days,
5. history of ARDS in the previous month,
6. body-mass index higher than 40 kg/m²,
7. intracranial hypertension,
8. broncho-pleural fistula,
9. chronic respiratory diseases requiring long-term oxygen therapy or respiratory support,
10. pulmonary fibrosis with a vital capacity < 50% (severe or very severe),
11. patients who are moribund or facing end of life and

12. receiving or planned to receive veno–venous, veno–arterial or arterio–venous extracorporeal membrane oxygenation (ECMO),
13. patients who receive invasive ventilation in home setting due to a neurological disease,
14. previously randomized in this study,
15. no informed consent.

4.4 Sample size calculation

Randomized controlled trial

A sample of 538 patients (269 per group) is needed to detect an absolute between-group difference in 90-day mortality of 10% in favor of the intervention group, assuming a 27% mortality in the control group, with a power of 80% at a two-tailed significance level of 0.047. In the sample size calculation, an interim analyses of the primary endpoint has been taken in account when 269 patients have completed the study (p-value of 0.003).

Pilot phase of the RCT

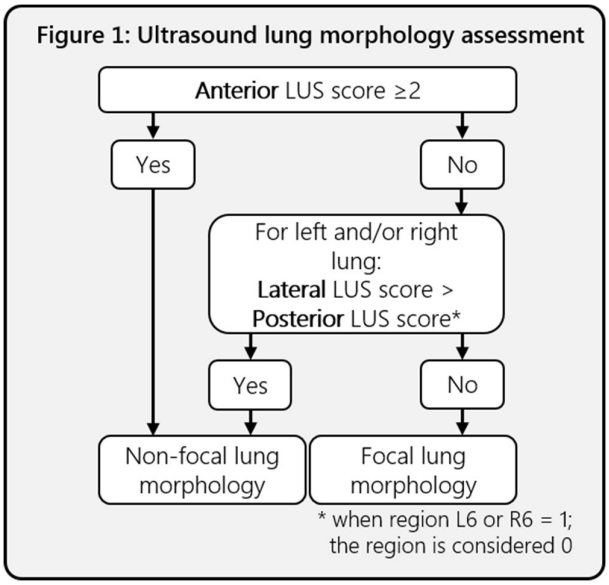
The pilot phase will comprise the first 80 included patients. We stated beforehand that at least 20 patients in each personalized group are necessary to assess clinical feasibility and protocol adherence. As the expected ratio between 'focal' and 'non-focal' and the ratio between the intervention and control group is 1:1, we would need a sample size of 80 patients for this pilot study. We expect an interobserver agreement among experts of κ: 0.85[17]. To be able to detect a clinically relevant decrease of κ towards 0.7 between experts and bedside clinicians, a total of 77 patients is needed for a power of 80% at a one-sided α level of 0.05. The primary endpoint will not be evaluated in the analysis of the pilot phase.

5 TREATMENT OF SUBJECTS

5.1 Investigational treatment

Patient who meet all of the inclusion criteria and none of the exclusion criteria will receive a LUS exam (APPENDIX III) within 12 hours of ARDS diagnosis to determine lung morphology using the algorithm presented in Figure 1. Patients will be randomly assigned to the intervention group, with personalized mechanical ventilation, or the control group, in which patients will receive standard care. If a patient is assigned to the intervention group, ventilator settings will be adjusted (Table 1) based on the lung morphology. LUS will be repeated every 48-72 hours in supine position for the focal ARDS patients in the personalized ventilation group to assess whether they have developed non-focal ARDS during admission. In that case, patients will from then on be treated according non-focal personalized treatment protocol. The FiO_2 is set according to the attending physician to reach the correct oxygenation targets (SpO2 and PaO2 are 88% to 95%, and 7.3 kPa to 10.7 kPa, respectively). Recommended duration of prone position is 16 hours. Recruitment maneuvers in the non-focal ARDS group will be performed daily as described in APPENDIX IV. Personalized ventilation will no longer be used if the treating physician expects extubation within 48 hours.

Figure 1: Ultrasound lung morphology assessment



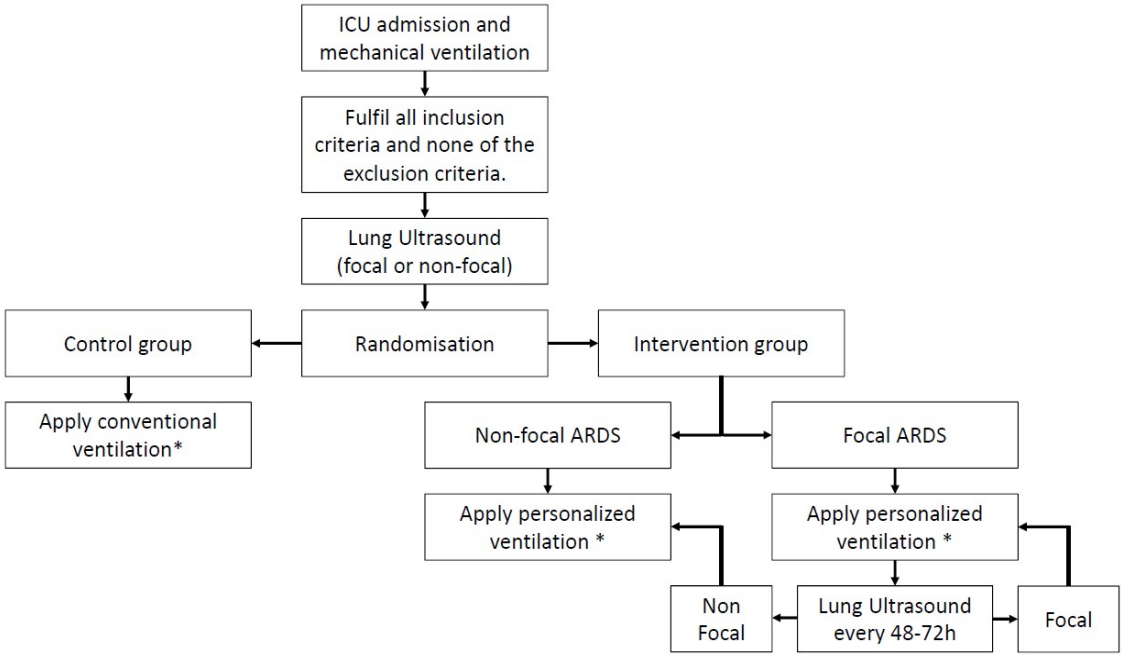


*Figure 2. Flow diagram PEGASUS. * ventilation strategy in table 1*

5.2 Control group

Patients assigned to the control group will be ventilated according to the current standard of care (Table 1). In these patients, the PEEP level will be selected according to the low PEEP/ high FiO_2 ratio from the ALVEOLI study maintaining an end-inspiratory plateau pressure (Pplat) lower than 30 cmH_2O[18] (Table 2). Prone position is encouraged if PaO_2/FiO_2 ratio is ≤ 150 and preferably 16 hours a day. Recruitment maneuvers are used as rescue therapy (APPENDIX IV).

5.3 Rescue therapies

In the event that maximum treatment in the personalized ventilator group is not sufficient, the protocol can be deviated from. These rescue therapies are defined in APPENDIX VIII.

Table 1 *Ventilation strategy for randomization and lung morphology group*

	Control group, standard of care	**Personalized group**	
		Focal	Non-focal
Mode of ventilation	Pressure controlled, volume controlled or pressure support	Pressure controlled, volume controlled or pressure support	Pressure controlled, volume controlled or pressure support
Tidal volume	6 mL/kg PBW	6 to 8 mL/kg PBW	4 to 6 mL/kg PBW
PEEP	Table 2	≤ 9 cm H_2O	≥ 15 cm H_2O
Recruitment maneuver	Only for rescue	Only for rescue	Daily*
Prone positioning	PaO_2/FiO_2 < 150	Daily	Only for rescue

PBW = predicted body weight, PEEP = positive end-expiratory pressure, FiO_2 = fraction of inspired oxygen, Pplat = end-expiratory plateau pressure, PSV = pressure support ventilation, PCV = pressure controlled ventilation.
* APPENDIX IV

Table 2 *FiO_2 and PEEP strategy for the control group*

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

FiO_2 = Fraction of inspired oxygen, PEEP = positive end-expiratory pressure.

5.4 General treatment of subjects

Standard ventilator management

The PEGASUS trial allows the following ventilator modes: pressure–controlled, volume-controlled ventilation and pressure support ventilation. Automated modes are allowed if the PEEP setting is restricted according to the protocol. With controlled modes of ventilation the default inspiration–to–expiration ratio is 1:2. With pressure support ventilation, the highest possible pressure rise is chosen and cycling off is set at 25% as default. Formula for calculating the tidal volume size with predicted body weight (PBW)[19] are 50 + 0.91 x (centimeters of height – 152.4) for males and 45.5 + 0.91 x (centimeters of height – 152.4) for females. The respiratory rate is adjusted to obtain an arterial blood pH >7.25 but preferably under the 35 breaths per minute. Default settings are indicative as starting point and can be adjusted at the discretion of the treating physician.

Oxygenation targets

The oxygenation target ranges for SpO_2 and PaO_2 are 88% to 95%, and 7.3 kPa to 10.7 kPa, respectively.[19] Oxygenation will be maintained in the target ranges primarily by adjusting the FiO_2 in the personalized groups and according to PEEP/FiO_2 table in the standard of care group (see sections 5.1 and 5.2). The oxygenation target is primarily assessed by peripheral saturation (SpO2) as measured by pulse oximetry and only in case of unreliable reading the oxygenation will be assessed by the arterial blood oxygen pressure (PaO2). For patients in whom the risk of potentially dangerous hypoxemia could be become unacceptable during the trial the oxygenation target range can be increased at the discretion of the treating physician.

Weaning from the ventilator

If extubation is expected within 48 hours in the personalized ventilation group, the PEEP level can reduced (non-focal group) or prone position can be stopped (focal group). Acceptance of assisted ventilation is tested three times a day in all patients who receive controlled ventilation. The attending physician decides when to extubate a patient, based on general extubation criteria (i.e. responsive and cooperative, adequate cough reflex, adequate oxygenation with $FiO_2 \leq 0.4$, hemodynamically stable, no uncontrolled arrhythmia and a rectal temperature > 36 Celsius and after successfully passing a spontaneous breathing trial (SBT) with a T–piece or ventilation with minimal support (pressure support level < 10 cm H_2O). In case SBTs are used, an SBT is judged as successful when the following criteria are met for at least 30 minutes, the attending physician takes the final decision for extubation:

- Respiratory rate < 35/min
- Peripheral oxygen saturation > 90%
- Increase < 20% of Heart rate and blood pressure
- No signs of anxiety and diaphoresis

In case a patient needs to be re–intubated and ventilated, the PEEP level is set as described in the treatment protocol.

Tracheostomy

Early tracheostomy has no advantage over late tracheotomy[21]. Therefore, tracheostomy is only to be performed on strict indications and preferably not earlier than 10 days after intubation. Strict indications for tracheostomy:

- Expected duration of ventilation > 14 days
- Glasgow Coma Score < 7 and/or inadequate swallow or cough reflex with retention of sputum
- Severe ICU–acquired weakness
- Repeated respiratory failure after extubation
- Pre–existent diminished pulmonary reserves
- Failure to intubate
- Prolonged or unsuccessful weaning

Weaning with a tracheostomy follows recommendations as described under ‘weaning’, a suggested scheme for unassisted ventilation with a tracheostomy is described in APPENDIX V.

Ventilator settings when a patient requires ECMO

In the event that a patient receives ECMO, the ventilator is set according to the local protocol for ventilation under ECMO. This means that PEEP is no longer titrated according to the study protocol.

Sedation protocol

Sedation follows the local guidelines for sedation in each participating unit. In general, these guidelines favor the use of analgo–sedation over hypno–sedation, use of bolus over continuous infusion of sedating agents, and the use of sedation scores. Nurses determine the level of sedation at least 3 times per day. The adequacy of sedation in each patient is evaluated using a Richmond Agitation Sedation Scale (RASS)[22,23]. A RASS score of –2 to 0 is seen as adequate sedation. The goals of sedation are to reduce agitation, stress and fear; to reduce oxygen consumption (heart rate, blood pressure and minute volume are measured continuously); and to reduce physical resistance to– and fear of daily care and medical examination. The use of neuromuscular blockage is not recommended. Patient comfort is the primary goal. Level of pain is determined using scales such as Numeric Rating Scale (NRS), Visual Analogue Scale (VAS), Critical Care Pain Observation Tool (CCPOT) or Behavioral Pain Scale (BPS).

Ventilator associated pneumonia prevention

If patients are expected to need ventilation for longer than 48 hours and/or are expected to stay in de ICU for longer than 72 hours, preventive measurements must be taken to prevent a ventilator associated pneumonia according to the local guidelines.

Fluid regimens

A fluid balance targeted at normovolemia and a diuresis of ≥ 0.5 ml/kg/hour should be maintained with diuretics or by crystalloid infusions, preferred over colloid infusions.

Thrombosis prophylaxis

Thrombosis prophylaxis is indicated for all patients who are not treated with anticoagulants, e.g. for therapeutic reasons or systemic prophylaxis because of an implanted device or extracorporeal circulation like for renal replacement therapy. Thrombosis prophylaxis will be given according to local guidelines.

Nutrition

Enteral nutrition with a feeding gastric tube is preferred over intravenous feeding. If stomach retention occurs, a duodenal tube can be used if administration of prokinetic drugs is not sufficient, according to local guidelines. When optimal protein intake cannot be reached within 4 days, additional parenteral nutrition can be started.

6 METHODS

6.1 Main study parameter/endpoint

The primary endpoint of this study is all-cause mortality at day 90 (diagnosis of ARDS considered as day 0).

6.2 Secondary study parameters/endpoints

Secondary study endpoints are mortality at 28 days, ventilator free days (VFD) at day 28 (with a penalty to mortality within 28 days to -1 days instead of 0 days), ICU length of stay, ICU mortality, hospital length of stay, hospital mortality and number of patients with complications.

6.3 Pilot phase parameters/endpoints

Endpoints of the pilot phase of the study are:

1. clinical feasibility of the standardized LUS exam in a multicenter setting when performed by the treating physician measured by (A) the time needed to perform a LUS exam, (B) the practicality of LUS in the proposed setting and (C) percentage of correct performed LUS exams.
2. interobserver agreement between the treating physician and an expert panel about the interpretation and the assessment of lung morphology of the LUS images.
3. protocol adherence according to the lung morphology and randomization groups (standard of care or personalized strategy) measured by (A) willingness of clinicians to randomize patients (patients randomized vs eligible); (B) willingness of patients' family to participate; (C) acceptability of the intervention to the users and (D) availability of the data needed and follow-up rate.
4. all recurrent events of exceeding 'safe limits' of mechanical ventilation (Pplateau > 30 cm H_2O and TV > 10mL/kg in a controlled ventilation mode), ventilator associated pneumonia and pneumothorax (APPENDIX VI).

6.4 Randomization, blinding and treatment allocation

Screening

Patients in participating centers are daily screened for eligibility after the start of invasive mechanical ventilation by the treating physician. Exclusion criteria are evaluated and, if applicable, the reason for exclusion is recorded.

Randomization

Patients will be randomized immediately after the LUS exam that will be performed within 12h after diagnosis of ARDS. Patients will be randomly assigned to the personalized ventilation arm or to the control arm with a 1:1 ratio. Clinical research platform Castor EDC (https://www.castoredc.com/) will be used to perform the randomization and is GCP and FDA compliant. Randomization will be done in blocks of randomly permuted size and stratified by center.

Blinding

As the patients in the two intervention groups require different actions from the treating physicians and nurses (e.g. prone position or recruitment maneuvers), blinding of the clinical staff is impossible. Important to note is that the LUS results in the control group will not be available for the clinical team as it will not be recorded in the patient file but only in the online case record form. Data analysis will be performed while blinded for the study intervention.

6.5 Data collection

- Direct at the diagnosis of ARDS (day 0) and within the first 24h of inclusion:
    - gender and age (male + years);
    - height and weight (cm + kg);
    - cause of ICU admission (sepsis, septic shock, hemorrhagic shock, coma, intra-abdominal sepsis, acute respiratory failure, acute metabolic disorders, elective surgery, urgent surgery);
    - cause of ARDS (Pneumonia, non-pulmonary sepsis, aspiration of gastric contents, major trauma, pulmonary contusion, pancreatitis, inhalation injury, severe burns, non-cardiogenic shock, drug overdose, TRALI, pulmonary vasculitis, drowning and other cause);
    - result of LUS exam (focal or non-focal ARDS) and images;

- if present, result of CT-scan (focal or non-focal ARDS, APPENDIX VII)
- Use of steroids (yes/no);
- Clinical frailty score (APPENDIX VI);
- APACHE II, APACHE IV, SAPS II and SOFA score; and
- Charlson Co-morbidity index.

- Every day at a fixed time point (around 8:00) until day 7, day 14, day 21, day 28 and at day 90:
  - life status (alive or deceased),
    - If deceased: report date and time.
  - if alive, location;
    - intensive care;
    - hospital ward; or
    - outside of the hospital
  - if hospitalized, invasiveness of ventilation;
    - no oxygen therapy;
    - oxygen by mask or nasal prongs;
    - oxygen by high flow nasal oxygen (HFNO) or non-invasive ventilation (NIV);
    - Mechanical ventilation, PaO_2/FiO_2 ≥150;
    - Mechanical ventilation PaO_2/FiO_2 <150 or vasopressors; or
    - Mechanical ventilation PaO_2/FiO2 <150 and vasopressors, dialysis, or ECMO.
  - Events and complications;
    - ventilator associated pneumonia (n) (APPENDIX VII);
    - pneumothorax (n) (APPENDIX VII);
    - use of ECMO (days);
    - use of renal replacement therapy (days);
    - inhaled vasodilators (yes/no);
    - airway pressure release ventilation (yes/no); and
    - tracheostomy (yes/no);
- On admission, and every day at a fixed time point (around 08:00), until day 7:
  - if invasive ventilation is applied;
    - mode of ventilation;

- tidal volume (mL);
- positive end–expiratory pressure (PEEP) (cm H_2O);
- plateau pressure (Pplat) and peak pressure (Ppeak) on volume controlled modes, maximum airway pressure (Pmax) on pressure controlled modes, or level of pressure support (PS) above PEEP (cm H_2O) on pressure support ventilation;
- inspired fraction of oxygen (FiO_2) (%);
- measured respiratory rate (RR) (min-1);
- pulmonary compliance (mL/cmH_2O) (tidal volume(ml)/(Pplat - PEEP (cmH_2O));
- recruitment maneuver (number) (APPENDIX VII);
- prone positioning (yes with hours or no) (APPENDIX VII); and
- for the personalized focal ventilation group: LUS exam every 48-72 hours in supine position (focal or non-focal ARDS).

o if location of patient is on the ICU;

- arterial pH;
- arterial bicarbonate (mmol/L);
- lactate (mmol/L);
- arterial partial pressure of oxygen (PaO_2) (kPa or mmHg);
- arterial partial pressure of carbon dioxide ($PaCO_2$) (kPa or mm Hg);
- arterial saturation of oxygen (SaO_2) (%);
- peripheral oxygen saturation (%);
- end-tidal fraction CO_2 (kPa);
- daily cumulative fluid balance (mL);
- Richmond Agitation-Sedation Scale (RASS) score;
- SOFA score.

- At day 90:
  - Clinical frailty score (APPENDIX VI).

6.6 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without consequences.

6.7 Follow-up of subjects withdrawn from treatment

Patients withdrawn from the trial will not be subjected to follow–up.

6.8 Replacement of individual subjects when deferred consent could not be obtained.

A randomized subject will be replaced if deferred consent is not obtained after randomization and provisional inclusion of a patient. In the randomization log, these cases will be recorded without patient-specific data.

7 SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 Endpoints for safety

The risks are considered to be minimal because the ventilation methods in the intervention group are already being applied in the standard care of ARDS patients. For this reason, we are not expecting Serious Adverse Events (SAEs) related to the study. LUS is a simple, non-invasive and safe form of imaging which is well tolerated by patients. Furthermore, the study population consists of critically ill patients, with a high incidence of death or life–threatening events due to the severity of their illness (the hospital mortality in ventilated ICU patients with ARDS is around 30%). Therefore, we propose to report the secondary endpoints of this trial, which incorporate ventilation specific complications, in a line listing two times per year to the METC to monitor safety of both treatment strategies. The METC will receive a line listing of the secondary endpoints incorporating ventilation specific complications (see below). These endpoints will be specified per study arm in the line listing without disclosing the specific arms.

Those ventilation specific complications include:

- ICU mortality;
- incidence of pneumothorax (APPENDIX VII);
- Suspected ventilatory associated pneumonia (APPENDIX VII).

7.3 Data Safety Monitoring Board (DSMB) / Safety Committee

A DSMB will be installed to monitor safety and the overall conduct of the trial. The DSMB will compose of 4 individuals who will be invited, one of which will be assigned as the chair.

- The DSMB will first meet after inclusion of the first 80 patients in the pilot phase, approximately 6 months after the first patient is enrolled.
- Subsequent to this meeting, the DSMB will meet virtually every 6 months.
- The DSMB will review the overall status of the program, number of patients enrolled overall and, in each center, adherence to the protocol overall and by each center.
- The DSMB will monitor safety of both ventilation strategies by monitoring the secondary endpoints of ventilation specific complications.

The report and/or advice of the DSMB will only be sent to the sponsor of the study, the Amsterdam University Medical Center (UMC), location 'Academic Medical Center' ('AMC'). Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

8 STATISTICAL ANALYSIS

8.1 General considerations

The statistical analysis will be based on the intention–to–treat principle, with patients analyzed according to their assigned treatment arms, except for cases lost to follow–up, or patients who are withdrawn due to lack of deferred informed consent. In addition, we will conduct per–protocol analyses, which only considers those patients who completed the treatment according to the originally allocated protocol.

When appropriate, statistical uncertainty will be expressed by the 95% confidence levels. P–value under 0.047 will be considered statistically significant for the primary study parameter and a p-value under 0.05 for secondary study parameters. Normality of data distribution will be assessed by visual inspection of histograms. For the experimental and control arms, continuous normally distributed variables will be expressed by their mean and standard deviation (SD) or, when not normally distributed, as medians and their interquartile ranges (IQR). Categorical variables will be expressed as frequencies and percentages. If less than 5% of data are missing or unavailable, no imputation data will be applied.

All statistical analyses will be described in full detail in a statistical analysis plan, which will be published before the database is locked and analysis starts. Analysis will be performed with R software.

8.2 Primary study parameter(s)

The goal of the primary analysis is to quantify the effect of LUS guided personalized mechanical ventilation vs. routine care on the 90-day mortality (with day of ARDS diagnosis as 0). The odds ratio between for 90-day mortality is calculated using logistic regression analysis with mortality as dependent variable and randomization group as independent variable. Adjusted analysis will be performed according to EMA and FDA guidelines [24] with the strongly prognostic variables age, clinical frailty and PaO2/FiO2 at admission as covariables. The stratification variable (center) will be included as a random effect.

8.3 Secondary study parameter(s)

Since ventilator–free days is a highly skewed variable with a peak in -1 due to 28–day mortality, the mean ratio will be estimated using a generalized additive model for

location scale and shape (GAMLSS) considering a zero–inflated and transformed beta distribution and using the delta method to estimate the confidence interval. A competing risk proportional hazard models will be used to evaluate the difference in time to extubation (accounting for mortality as a competing risk).

A predefined subgroup analysis stratified per phenotype (focal and non-focal) will be performed between the randomization arms for all primary and secondary outcomes.

Differences between groups in continuous variables will be analyzed with Student's t–test or the Mann–Whitney U. Categorical variables will be compared with the Chi–squared test or Fisher's exact test, as appropriate. Mortality rates and length of ICU and hospital stay will be compared using Kaplan–Meier mortality curves.

8.4 Pilot phase parameters

To assess interobserver agreement, an expert panel will score all LUS exams to assess and evaluate the clinicians' diagnostic accuracy of distinguishing focal ARDS from non-focal ARDS by using Fleiss' κ. The expert panel will be blinded to the randomization group and clinical parameters of the patient while scoring the LUS exams.

Variables will be expressed as frequencies and percentages, means and SD or medians and IQR whenever appropriate (see paragraph 8.1) on the following ventilator settings; PEEP, Pplateau, Ppeak, Pmax, complications, prone position and recruitment maneuvers).

9 ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil 2013, in accordance with the Medical Research Involving Human Subjects Act (WMO) and comply with Good Clinical Practice (GCP) Guidelines and all applicable national (for example WMO for the Netherlands) and international regulatory requirements and general data protection regulations (GDPR).

9.2 Recruitment and consent

Deferred consent

For this study we ask for deferred consent and we appeal to the emergency procedure for consent in medical research as stated in article 6, paragraph 4 of the WMO. This deferred consent procedure has successfully been applied in three previously performed trials of ventilation in a similar patient cohort ('PRotective VENTilation in Patients without ARDS at Start of Ventilation – PReVENT, a Randomized Controlled Trial' (METC 2014_075), 'REstricted versus Liberal positive end–expiratory pressure in patients without Acute respiratory distress syndrome (RELAx) – a multicenter randomized controlled trial' (METC 2017_074), 'The Effect of Automated Closed-loop Ventilation versus Conventional Ventilation on Duration and Quality of Ventilation ('ACTiVE') - a randomized clinical trial in intensive care unit patients' (METC 2020_146)) and is also approved in the more recently study 'Effect of lung Ultrasound–guided Fluid Deresuscitation on Duration of ventilation in Intensive Care unit patients (CONFIDENCE)' (METC 2021_182), for reasons as explained below.

Almost all patients with ARDS that are admitted to an intensive care unit (ICU), urgently need invasive ventilation. Ventilator–related side–effects are seen after relatively short periods of ventilation, e.g., after ventilation during general anesthesia for surgery[25]. For this reason, we consider it of utmost importance to set the ventilator according to the study protocol in this study as soon as possible (i.e., within 12 hours after diagnosis of ARDS). Any other strategy would largely reduce the validity of the results of this study.

Patients admitted for ventilator support to the ICU are, without exception, not able to give informed consent. Persons who may take the role of legal representative

in accordance with the Medical Treatment Agreement Act (WGBO) are: a predefined representative, husband or wife, registered partner or other life partner, a parent or child, brother or sister, and incidentally a curator appointed by a judge. However, the legal representatives are frequently absent at the moment their beloved ones are admitted to or when ventilation starts in the ICU. Obtaining informed consent from a legal representative usually takes time, even by an experienced research team[26], as consent requires sufficient time to read and consider the provided written information. Moreover, legal representatives are far more concerned about the wellbeing of the patient then about participation in a trial in the period just after ICU admission or start of ventilation[27,28]. Finally, the experience of ICU patients enrolled under deferred consent is mainly positive. In the NICE-SUGER trial, in which participants were included using deferred consent, showed that a majority of the patients were happy with the decision made by the representative (93%) and would have granted consent if asked (96%)[29].

For these reasons, we opt for using deferred consent, where informed consent from a legal representative must be obtained as soon as possible, but always within 72 hours after randomization, confirmed written on paper. If informed consent is not obtained, or if a legal representative denies participation within the time window of 72 hours, the patient is excluded and data will no longer be used. Thenceforth the patient is ventilated according to the policy of the attending physician.

No deferred consent in patients who die before obtaining informed consent

In case a patient dies before informed consent could be obtained from the legal representative, we propose to use the data and inform the legal representative about the research without obtaining informed consent. This is in line with the advice from Jansen and colleagues regarding ethical validity and practical feasibility of deferred proxy consent in emergency critical care research and in line with the advice of the Central Committee on Research Involving Humans (CCMO, the Dutch national Ethics Committee) in these circumstances in the early lactate–directed therapy in the ICU[28,30].

The CCMO judged that the situation in which a patient dies before consent could be obtained is comparable to the situation in which the research project has already finished at the time deferred consent can be obtained. They concluded that the legal representative should be notified about the study, but that seeking consent was not useful anymore due to the lack of consequences for the patient, while it causes bias of

the study results. The representation of the patient by a legal representative ends when the patient dies. In the Dutch law, the consent of the patient or his/her relative primarily relates to the participation in the study and not to using the data collected in the study[28].

Informed consent after deferred consent

If deferred consent has been obtained and the patient is alive and competent for informed consent, then informed consent will be asked within 90 days after randomization. In the event that the patient declines informed consent, the collected data will be deleted.

9.3 Benefits and risks assessment, group relatedness

Protective mechanical ventilation in ARDS currently consists of low tidal volume ventilation with a hypoxemia driven level of positive end-expiratory pressure. Furthermore, prone positioning and recruitment maneuvers are frequently used in patients with persistent hypoxemia. There is extensive experience with these procedures in every ICU. These interventions can be beneficial but can also cause harm, leading to many 'no benefit' of clinical trial results in unselected populations. LUS is a safe imaging technique that is widely applied in ICU's and has shown good accuracy for identifying lung morphology. Using this technique, it is likely that we can select patients who will benefit from recruitment or prone positioning in order to improve outcomes.

9.4 Compensation for injury

The sponsor has liability insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of June 23, 2003). This insurance provides cover for damage to research patients through injury or death caused by the study.

This insurance provides cover for damage to research patients through injury or death caused by the study.

- € 650.000 (i.e. six hundred and fifty thousand Euro) for death or injury for each patient who participates in the Research.
- € 5.000.000 (i.e. five million thousand Euro) for death or injury for all patients who participate in the Research.

€ 7.500.000 (i.e. seven million and five hundred thousand Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All patients will be addressed to the interventions with a random patient identification code. The codebook will be stored digitally. The paper version will be stored behind a lock and the digital form will be encrypted with a double password. All data will be stored for the length of the study and for 15 years afterwards. All handling of personal date will comply with the General Data Protection Regulation (AVG). Data can be shared between participating hospitals. Only coded information will be shared using data sharing systems developed for sharing medical data.

10.2 Data entry into the electronic database

The complete paper CPIS score, for the diagnosis of VAP (appendix VII), are filed in the TMF/ISF folder (under tab O2). When no completed paper CPIS score is filed and the complication VAP is scored in Castor EDC, answers to the questions are directly entered in Castor EDC by the investigator from the electronic patient dossier.

10.3 Protocol deviations

Ventilation parameters show fluctuation over time due to the dynamic pathophysiology of the lungs in ARDS patients and due to temporary adjustment of ventilator settings during common ICU procedures. Small or short variations in ventilation parameters will not affect the intervention or outcome of the PEGASUS study and neither affect the safety of the patient. To avoid the need to report a large amount of insignificant protocol deviations, guidelines were created for documentation of protocol deviations (APPENDIX VIII).

10.4 Monitoring and Quality Assurance

Queries on the database will be done by a statistician and analyzed by the monitor to signalize early aberrant patterns, trends, issues with consistency of credibility and other anomalies.

On site monitoring will be performed by the Clinical Monitoring Center for all Dutch hospitals. The monitoring will compromise controlling presence and completeness of the research dossier and the informed consent forms and the performance of source data checks, as described in the monitoring plan. Every

participating center will be visited after the inclusion of the first ten patients, and thereafter at least once every year. A monitoring plan is being developed.

10.5 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited Medical Research Ethical Committee (METC, Dutch Medical Ethics Committee) has been given. The METC and the competent authority will be notified of all substantial amendments. Non–substantial amendments (typing errors and administrative changes) will not be notified to accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.6 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, unexpected problems and amendments.

10.7 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

The study can be ended prematurely by the steering committee based on recommendations of the DSMB, for example as a result of low recruitment. There is a formal stopping rule after the first interim analysis. If the threshold of P=0.003 is passed in favor of either of the treatment arms, the study is automatically ended. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/ sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.8 Public disclosure and publication policy

The study protocol will be registered before inclusion of the first patient on Clinicaltrials.gov. The results of the study will find their way into (inter–) national

scientific journals and guidelines. We will submit analyses to scientific journals in the field of intensive care medicine or pulmonology.

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12 APPENDIXES

APPENDIX I - List of participating centers

1) University of Bari Aldo Moro, Italy.
2) Central Clinical Hospital of the Ministry of the Interior and Administration, Warszawa, Poland.

APPENDIX II - The Berlin Definition of ARDS

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest Imaging [a]	Bilateral opacities - not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation [b]	
Mild	200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥5cm H_2O[c]
Moderate	100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2×(barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

APPENDIX III – LUS Examination

The LUS examination is based on the most recent literature in the assessment of focal or non-focal ARDS by using LUS. The LUS exam is performed using a transversal approach with a linear probe at a PEEP level of 5 cm H_2O in semi-recumbent position. Use of other probes is allowed when use of the linear probe does not result in assessable LUS images. In the situation where too much decruitment is expected with a PEEP of 5 cm H_2O, the LUS exam can also be performed at a PEEP level of 8 cm H_2O. Twelve different regions of the lungs can assessed, six locations for each hemithorax (Figure 3). Every location is scored using the score system in Figure 4. The type lung morphology (focal of non-focal ARDS) is assessed using the algorithm in figure 1.

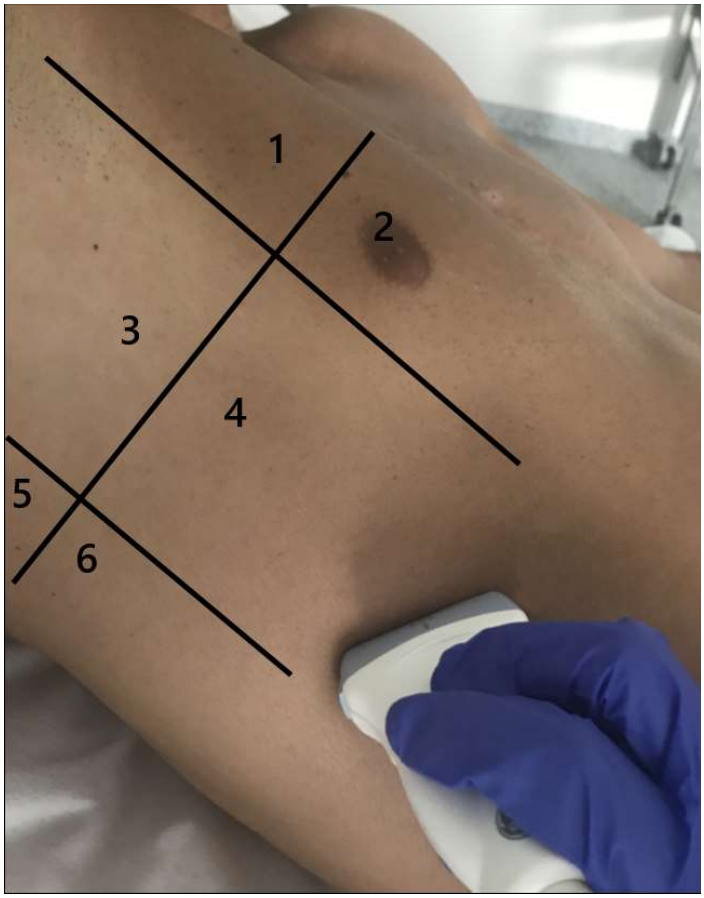

Figure 3. Six different regions of a hemithorax. Zones 1 and 2 are anterior LUS regions, zones 3 and 4 are lateral LUS regions, and zones 5 and 6 are posterior LUS regions.[17]

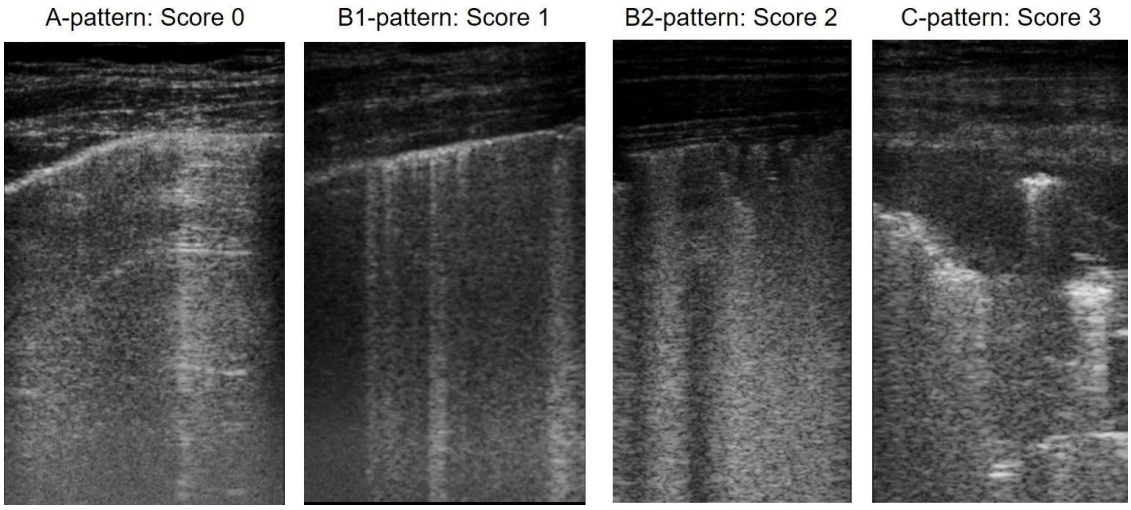

Figure 4. Score 0: "A-pattern" (i.e., repeating horizontal A-lines parallel to the pleural line, suggesting normal aeration). Score 1: a "B-pattern" (i.e., three or more vertical B-lines starting from the pleural line and reaching the bottom of the screen, suggesting partial loss of aeration) and B-lines are well-spaced and cover ≤ 50% of the pleural line, Score 2: if B-lines cover ≥ 50% of the pleural line. Score 3: a "C-pattern" (i.e., consolidation, suggesting near-complete to complete loss of aeration).[17]

APPENDIX IV - Recruitment maneuver

1) The RM is performed by a qualified person, i.e., an intensivist of an intensive care doctor with sufficient experience;

2) Set PEEP at a minimum of 15 cm H_2O; if PEEP was not yet at 15 cm H_2O, it is increased in steps of 1 to 2 cm H_2O, wherein each steps last at least 10 seconds to see if the blood pressure remains acceptable. hemodynamic instability occurs; if PEEP is already > 15 cm H_2O, it is left unchanged;

3) Perform an inspiratory hold of 10 seconds by pressing the inspiratory hold button for 10 seconds; closely monitor the blood pressure, as if it drops the rescue maneuver is stopped to take measure to ensure hemodynamic stability (e.g., by raising the dose of vasoactive medication);

4) In successive steps, set the upper airway pressure 15 cm H_2O above PEEP, followed by an inspiratory hold of 10 seconds by pressing the inspiratory hold button for 10 seconds; closely monitor the blood pressure, as if it drops the rescue maneuver is stopped to take measure to ensure hemodynamic stability (e.g., by raising the dose of vasoactive medication);

5) This maneuver is repeated 3 times;

5) At PEEP of 15 cm H_2O, the upper airway pressure is set in such a way that the tidal volumes again corresponds to the ventilation settings of the randomization arm.

APPENDIX V – Scheme for unassisted ventilation with tracheostomy

The following suggested scheme can be used for unassisted ventilation with a tracheostomy, but should be individualized in every patient:

1. Unassisted ventilation for 30 minutes, three times per day
2. Unassisted ventilation for 1 hour, three times per day
3. Unassisted ventilation for 2 hours, three times per day
4. Unassisted ventilation for 4 hours, three times per day
5. Unassisted ventilation for 6 hours, two times per day
6. Unassisted ventilation for 18 hours
7. Unassisted ventilation for 24 hours

APPENDIX VI - Clinical Frailty Scale

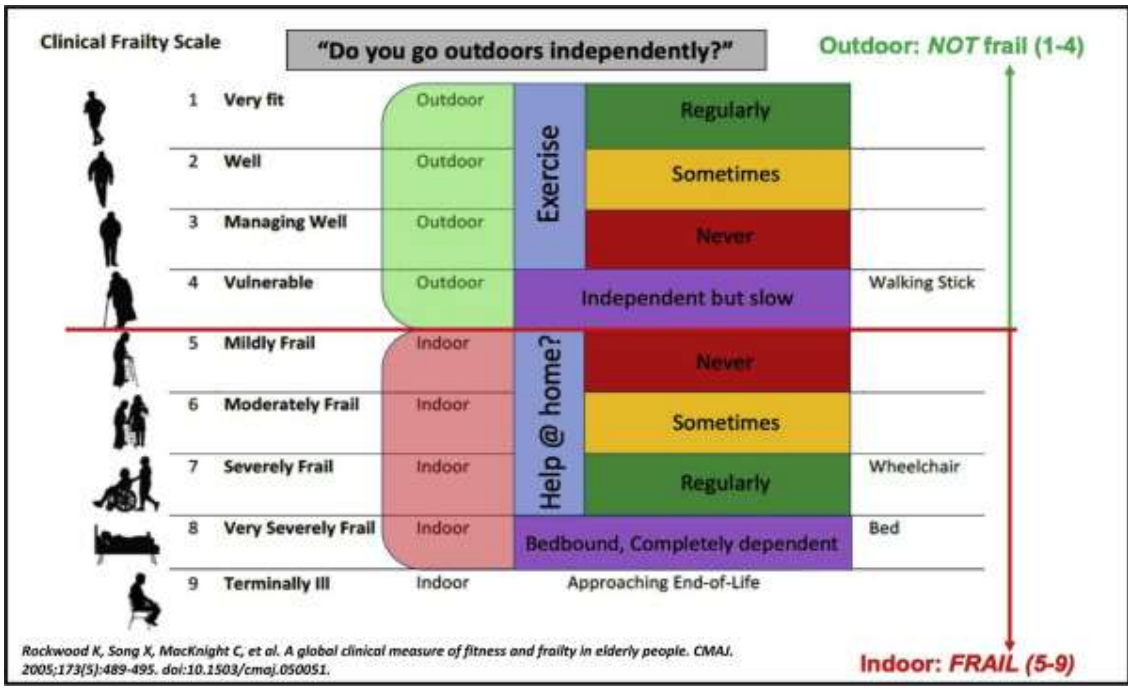

Figure 5. Clinical frailty scale for emergency departments. Patients are scored at admission and, if possible, at day 90. The score ranges from 1 until 9.[31]

APPENDIX VII - Definitions

- Ventilator–free days and alive at day 28 (VFD–28):
  - VFD–28 = -1 if subject dies within 28 days of mechanical ventilation
  - VFD–28 = 28 – x if successfully liberated from ventilation x days after initiation
  - VFD–28 = 0 if the subject is mechanically ventilated for ≥ 28 days
- Ventilator Associated Pneumonia (VAP): Clinical Pulmonary Infection Score (CPIS, table 3) > 5 with an infiltration on CXR.

Clinical Pulmonary Infection Score	Points
Body temperature	
≥ 36.5 or ≤ 38.4	0
≥ 38.5 or ≤ 38.9	1
≥ 39 or ≤ 36.4	2
Leucocyte count	
≥ 4.0 or ≤ 11.0 $\cdot 10^9 \cdot L^{-1}$	0
< 4.0 or > 11.0 $\cdot 10^9 \cdot L^{-1}$	1
Rod form ≥ % 50	Add 1 point
Tracheal secretion	
Absence of tracheal secretion	0
Presence of tracheal secretion	1
Abundant purulent secretion	2
Oxygenization	
$Pa0_2/Fi0_2$, mmHg > 240 or ARDS present	0
Pa02/Fi02, mmHg ≤ 240 or no ARDS	2
Pulmonary infiltration in chest X-ray	
No infiltration	0
Diffuse infiltration	1
Localized infiltration	2
Progression in pulmonary infiltration	
Radiographic progression (-)	0
Radiographic progression* (+) *After exclusion of Heart failure and ARDS	2
Pathogenic bacteria in tracheal aspirate culture	
No or few pathogenic bacteria	0
Moderate or high levels of pathogenic bacteria	1
Pathogenic bacteria to be seen in Gram staining	Add 1 point

- Pneumothorax: air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiograph or other kind of imaging suitable for diagnosis pneumothorax.
- Prone position: will have a duration of at least 16 hours.
- Phenotype on CT-Thorax: Focal morphology is defined as isolated consolidations with an infero-dorsal dominance. Non-focal morphology is defined as presence of diffuse or patchy opacifications, with or without dorsal consolidations[9].

APPENDIX VIII – Ventilation margins and rescue interventions.

Acceptable ventilation margins for the control/standard care group:

- A deviation in PEEP level of +/- 3 cmH_2O OR FiO_2 of +/- 10% from the proposed setting in the PEEP and FiO_2 table.
- During interventions (e.g. bronchoscopy, placing patient in prone positioning) the FiO_2 can be raised for a period of time without raising the PEEP.
- In a controlled ventilation mode, the margins for the tidal volumes are allowed to range from 4 – 8 ml/kg PBW. In modes of ventilation that allows spontaneous breathing, such as pressure support ventilation, the tidal volume targets can be released.

Acceptable ventilation margins and rescue interventions in the group with personalized ventilation and focal ARDS:

- If the FiO2 is higher than 80% and the PaO_2/ FiO_2 is below 100 mmHg in prone position for more than 6 hours the physician is allowed to set the PEEP above 9 cm H_2O and recruitment maneuvers can be applied.
- In modes of ventilation that allows spontaneous breathing, such as pressure support ventilation, the tidal volume targets can be released.

Acceptable ventilation margins and rescue interventions in the group with personalized ventilation and non-focal ARDS:

- PEEP can be set lower than 15 cm H_2O when the plateau pressure is > 30 cm H_2O.
- Prone positioning can be applied when the PaO_2/FiO_2 is lower than 150 mmHg for 6 hours in supine position and the FiO_2 is > 80%.
- If the patient is breathing spontaneously, PEEP can be decreased to 10 cm H_2O and recruitment maneuvers are now only performed at the physicians discretion.

In modes of ventilation that allows spontaneous breathing, such as pressure support ventilation, the tidal volume targets can be released.