RESEARCH PROTOCOL

Effect of lung Ultrasound–guided Fluid Deresuscitation on Duration of ventilation in Intensive Care unit patients (CONFIDENCE)

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PROTOCOL TITLE: EffeCt of lung ultrasOuNd–guided Fluid deresuscItation on Duration of vEntilation iN intensive Care unit patiEnts (CONFIDENCE).

Protocol ID	CONFIDENCE 6.0
Short title	Lung ultrasound–guided fluid deresuscitation in ICU patients
Version	6.0
Date	May 17, 2022
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LIST OF ABBREVIATIONS

ARDS	**Acute Respiratory Distress Syndrome**
BNP	**Brain Natriuretic Peptide**
BPS	**Behavioral Pain Scale**
CCPOT	**Critical Care Pain Observation Tool**
CPAP	**Continuous positive airway**
CXR	**Chest X-ray**
DSMB	**Data Safety Monitoring Board**
FDA	**Food and Drug Administration**
FiO_2	**Fraction of Inspired Oxygen**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IC	**Informed Consent**
ICU	**Intensive Care Unit, patientcare under supervision of an intensivist**
LOS	**Length Of Stay**
LUS	**Lung UltraSound**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NRS	**Numeric Rating Scale**
$PaCO_2$	**Partial Pressure of Carbondioxide**
PaO_2	**Partial Pressure of Oxygen**
PBW	**Predicted Body Weight**
PEEP	**Positive End Expiratory Pressure**
PEEP	**Positive End Expiratory Pressure**
PiCCo	**Pulse Contour Cardiac Output**
RASS	**Richmond Agitation Sedation Scale**
RCT	**Randomised Clinical Trial**
RRT	**Renal Replacement Therapy**
SDD	**Selective Decontamination of the Digestive tract**
SOD	**Selective Oropharyngeal Decontamination**
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.
TPN	**Total Parenteral Nutrition**
VAS	**Visual Analogue Scale**
VFD	**Ventilator Free Days**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale

Timely recognition and treatment of fluid overload can expedite liberation from invasive mechanical ventilation in critically ill intensive care unit (ICU) patients. Lung ultrasound (LUS) is an easy to learn, safe, cheap and noninvasive bedside imaging tool with high accuracy for pulmonary edema and pleural effusions in ICU patients.

Objective

The aim of this study is to assess the effect of LUS–guided deresuscitation on duration of invasive ventilation in ICU patients.

Hypothesis

We hypothesize that LUS–guided fluid deresuscitation is superior to routine fluid deresuscitation (not using LUS) with regard to duration of invasive ventilation.

Study design

A national multicenter randomized clinical trial (RCT) in invasively ventilated ICU patients.

Study population

This study will include 1,000 consecutively admitted invasively ventilated adult ICU patients, who are expected not to be extubated within the next 24 hours after randomization.

Intervention

Patients are randomly assigned to the intervention group, in which caregivers are guided by repeated LUS in fluid deresuscitation, or the control group, in which fluid deresuscitation is at the discretion of the treating physician.

Main study parameters/endpoints

The number of ventilator–free days and alive at day 28 (primary); total duration of ventilation, ICU– and hospital length of stay; ICU–, hospital–, and 28–day and 90–day mortality rates, incidence of reintubations, cumulative fluid balance at successive days; proportion of patients who develop kidney injury.

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

Patient burden and risks are low, the collection of general data from hospital charts and (electronic) medical records systems causes no harm to the patients; daily LUS does not cause discomfort.

1 INTRODUCTION

1.1 Fluid resuscitation and deresuscitation

Current guidelines recommend aggressive fluid *resuscitation* in hemodynamic instable intensive care unit (ICU) patients, an approach that often leads to a positive cumulative fluid balance, pulmonary edema and pleural effusion[1,2]. Pulmonary edema is a strong and independent predictor of death[2-4]. Delayed fluid *deresuscitation* is independently associated with a longer need for invasive ventilation, and consequently a longer stay in the ICU[5-7].

1.2 Early and expeditious versus gradual deresuscitation

Decisions on timing and speed of *deresuscitation* are challenging. Caregivers usually weigh the benefits and risks of 'early and expeditious' versus 'gradual' *deresuscitation*. With 'early and fast' *deresuscitation*, in an attempt to reduce pulmonary edema, fluid infusions are restricted when weaning from vasopressors has started, and fluid withdrawal starts as early as possible thereafter[8,9], most often until a neutral fluid balance has been achieved. With 'gradual' *deresuscitation*, fluid infusion is restricted not before a (nearly complete) weaning from vasopressors has been achieved.

1.3 Recognition of pulmonary edema

Presence of pulmonary edema could be an additional trigger to start and determine extent of deresuscitation, but recognition of presence of pulmonary edema is challenging. Use of pulmonary artery catheters or pulse contour cardiac output (PiCCO) measurement techniques could help, but these techniques are expensive, complex, and invasive[10]. Chest radiography is cheap and simple, but has insufficient accuracy for pulmonary edema in invasively ventilated ICU patients[11].

1.4 Lung ultrasound

Lung ultrasound (LUS) is a simple and safe, cheap and noninvasive diagnostic imaging tool that has a high accuracy for pulmonary fluid overload[12]. While the presence of so–called 'A–lines' suggests the presence of normal lung tissue under the probe, the presence of multiple so–called 'B–lines' suggest abnormal lung tissue, most often because of pulmonary edema. In addition, lung ultrasound allows identification and quantification of pleural effusions. LUS of the anterior, lateral and dorsal chest regions

can help to semiquantify how ‘wet’ the lungs are[12,13]. Thus, LUS could guide decisions regarding *deresuscitation*. Presence of a ‘wet’ lung should trigger deresuscitation in hemodynamic stable patients. This may result in faster weaning from the ventilator, and consequently a shorter stay in ICU.

1.5 Current evidence

We recently piloted LUS–guided *deresuscitation* in 200 ICU patients and showed (a) this approach to be highly feasible (100% of patients)[14], (b) to lead to earlier start of *deresuscitation* (50% of patients), and (c) to reduce the cumulative fluid balance in ICU patients (66% of patients) (yet unpublished data).

1.6 Need for a study

The here proposed randomized clinical trial, named the ‘EffeCt of lung ultrasOuNd–guided Fluid deresuscItation on Duration of vEntilation iN intensive Care unit patiEnts’ (CONFIDENCE) will provide high level of evidence for benefit of LUS–guided *deresuscitation* strategy with regard to duration of ventilation in ICU patients.

1.7 Relevance for practice

The results of the here proposed study will be highly relevant for daily practice. The harm of a positive cumulative fluid balance and pulmonary edema is well recognized [1-7], whereas evidence on benefits of a more aggressive *deresuscitation* is growing [8,9,15].

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

LUS–guided fluid deresuscitation is superior to routine fluid deresuscitation (not using LUS) with regard to duration of invasive ventilation.

2.2 Primary objective

The primary objective of this trial is to compare LUS–guided deresuscitation to routine deresuscitation with respect to the number of ventilator–free days and alive at day 28.

2.3 Secondary clinical objectives

Secondary objectives include the comparison of LUS–guided deresuscitation to routine deresuscitation with respect to duration of ventilation, ICU– and hospital, and 28– and 90–day mortality, ICU– and hospital length of stay (LOS), incidences of reintubations, cumulative fluid balances at successive days and incidence of acute kidney injury (AKI).

3 STUDY DESIGN

The CONFIDENCE study is an investigator–initiated, national, multicenter, randomized clinical trial in critically ill invasively ventilated adult patients admitted to the ICUs of participating hospitals. The RCT will be conducted according to Good Clinical Practice (GCP) Guidelines and comply with the principles of the Declaration of Helsinki, all applicable national (for example WMO for the Netherlands) and international regulatory requirements and general data protection regulations (GDPR). The RCT will be registered in a public registry, and the study protocol with its statistical analysis plan will be published before enrollment of the first patient.

4 STUDY POPULATION

4.1 Population (base)

We will recruit eligible consecutive intensive care unit (ICU) patients. The ICUs of the (1) Academic Medical Center (Amsterdam) (2) VU Medical Center (Amsterdam), (3) Leiden University Medical Center (Leiden), (4) Catherina Hospital (Eindhoven), (5) Franciscus Gasthuis (Rotterdam), (6) Erasmus Medical Center (Rotterdam), (7) Radboud University Medical Center (Nijmegen), (8) Rijnstate Hospital (Arnhem), (9) Spaarne Gasthuis (Haarlem and Hoofddorp), (10) Onze Lieve Vrouwe Gasthuis (Amsterdam), will participate in the RCT. A total of 1000 patients will be randomized, approximately 100 patients per center.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

(a) admitted to one of the participating ICUs; and
(b) invasively ventilated for less than 24 hours at randomization; and
(c) expected to be under invasive ventilation for longer than 24 hours after randomization.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

(a) age < 18 years;
(b) pregnancy;
(c) participation in other interventional trials with similar endpoints;
(d) use of long term home mechanical ventilation;
(e) neurological condition that can prolong duration of invasive ventilation, i.e. Guillain-Barré syndrome, high spinal cord lesion, amyotrophic lateral sclerosis, multiple sclerosis, and myasthenia gravis;
(f) conditions in which LUS cannot be performed or correctly interpreted, i.e. chest wall abnormalities, morbid obesity, and pre-existing interstitial lung disease;
(g) conditions in which targeting a negative fluid balance is discouraged, i.e. subarachnoid bleeding, severe rhabdomyolysis (CK > 20.000);

(h) extracorporeal membrane oxygenation (ECMO);
(i) patients with severe burns;
(j) previous participation in this RCT;
(k) patients transferred from another center and invasively ventilated for longer than 24 hours.

4.4 Sample size calculation

The sample size is computed on the basis of the hypothesis that LUS guided deresuscitation is associated with a reduction of two days of ventilation. Assuming a mean (±SD) number of VFD-28 of 13±11 days [16,17], we estimate that a sample of 1000 patients (500 per group) is needed to have 80% power, at a two-tailed significance level of 0.05, to detect a mean between-group difference of 2 VFD-28, and allowing an anticipated dropout rate of 5%.

5 METHODS

Lung ultrasound (LUS) is a simple, safe, cheap, non-invasive diagnostic imaging tool with high accuracy for pulmonary fluid overload [11]. Presence of so-called 'A-line' artifacts suggests normal lung tissue under the probe, so-called 'B-lines' (≥3) suggest that lung tissue in the scanned region is edematous. LUS can even be used to identify and quantify the amount of pleural effusion. The sum of these findings in the anterior, lateral and dorsal chest regions is helpful to quantify how 'wet' the lungs of ICU patients are [13].

5.1 Investigational treatment

With LUS-guided fluid deresuscitation, LUS examinations are performed at least once a day with a recommendation of twice a day, in hemodynamically stable patients, defined as mean arterial pressure (MAP) ≥ 65 mmHg (with vasopressor dose clearly decreasing and norepinephrine ≤ 0.2 µg/kg/min), arterial lactate level < 2,5 mmol/L *or* < 4 mmol/L and decreased with > 25% in last hours**,** and no clear signs of hypoperfusion such as mottled skin and capillary refill time > 3 seconds and/or new oliguria (urine output < 0.3-0.5ml/kg/hour for the previous 6 hours). If some of these clinical signs are not related to hypoperfusion, these signs can be disregarded at the discretion of the treating physician. Target MAP can be waived in conditions in which 65 mmHg is not sufficient (i.e. history of chronic hypertension). In these cases the target MAP is at the discretion of the treating physician. 12-region LUS is performed, by a trained healthcare provider, and each region is scanned for the presence of B-lines and pleural effusions and scored using the lung ultrasound score (APPENDIX I). LUS examinations will be performed daily until discharge from the ICU or until day 28, whatever comes first.

<u>With every new LUS examination, the following scenarios, with distinct recommendations, are possible:</u>

Scenario 1. LUS suggests pulmonary edema. Pulmonary edema is defined as presence of bilateral B-profile (≥3 B-lines) or C-profile in anterior or lateral regions, i.e. lung ultrasound score of 1, 2 or 3 (APPENDIX I).

These LUS observations suggest massive pulmonary fluid overload, with the recommendation to minimize fluid infusion and start fluid withdrawal, targeting a negative fluid balance of at least -1500 ml in the next 24 hours;

Scenario 2. LUS suggests some pulmonary edema and/or significant pleural effusion. Some pulmonary edema is defined as unilateral presence of B-profile (≥3 B-lines) or C-profile in the anterior or lateral regions, i.e. lung ultrasound score of 1,2 or 3 (APPENDIX I). Significant pleural effusion is defined as > 1 cm in lateral regions, or > 2 cm in posterior regions.

These LUS observations suggest little pulmonary fluid overload, with the suggestion to minimize fluid infusion and start fluid withdrawal, targeting a negative fluid balance at least -500 ml in the next 24 hours;

Scenario 3. LUS suggests absence of pulmonary edema and no pleural effusion. Absence of pulmonary edema is defined as absence of B-profile (<3 B-lines) or C-profile in anterior or lateral regions, i.e. lung ultrasound score of 0 (APPENDIX I).

These LUS observations suggest no fluid overload, with the suggestion to target a neutral fluid balance in the next 24 hours.

<u>In between LUS examinations, the following scenarios, with recommendations, are possible:</u>

1. Patient remains stable. Fluid withdrawal is continued.
2. If hypotension develops, fluid withdrawal is decreased by 50% and vasopressor infusion is started, or increased. Fluid boluses are only given when vasopressor dosages become too high (norepinephrine > 0.2 µg/kg/min).
3. If hypotension combined with hypoperfusion, a small fluid bolus of 250 ml can be given, after which vasopressor infusion is increased. Fluid administration can be repeated at the discretion of the treating physician.

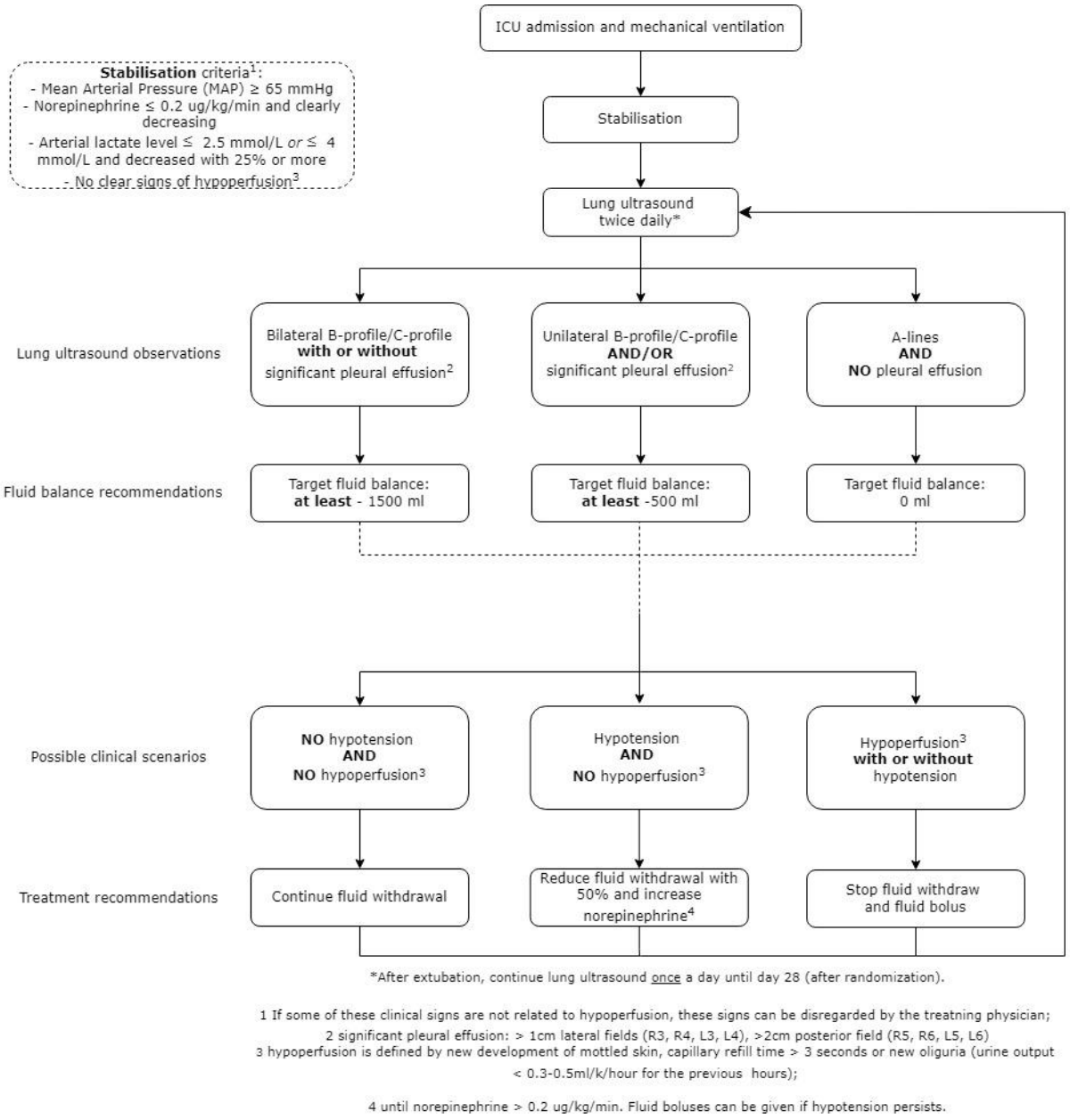

Figure 1: Flowchart of the investigational treatment. Insensible loss is not taken in to account for the fluid balance. Footnotes:[1] If some of these clinical signs are not related to hypoperfusion, these signs can be disregarded at the discretion of the treating physician; [2]Significant pleural effusion: > 1 cm lateral fields (R3, R4, L3, L4), > 2 cm posterior fields (R5, R6, L5, L6) [3] hypoperfusion is defined by new development of mottled skin, capillary refill time > 3 seconds, or new oliguria (urine output < 0.3-0.5ml/kg/hour for the previous 6 hours); [4] until norepinephrine > 0,2 µg/kg/min. Fluid boluses can be given if hypotension persists.

5.1.1 Additional therapy

- Choice of fluids is at the discretion of the treating physician. Crystalloid and balanced infusions are preferred over colloid infusions.
- Inodilator therapy, i.e., the combination of positive inotropic and vasodilating therapy, to improve cardiac output can be started at the discretion of the treating physician when deemed necessary.

- A chest drain may be placed at the discretion of the treating physician.
- In occurrence of hypernatremia intravenous administration of fluids should be switched from isotonic saline solution to 5% dextrose. As an alternative distilled water can be given enterally[18].
- In occurrence of rising creatinine levels without hypoperfusion fluid withdrawal should be continued and the target fluid balance remains unchanged.

5.1.2 Monitoring and treatment after extubation

After extubation, lung ultrasound is continued once a day until day 28 or until discharge (whatever comes first) to monitor reappearance of pulmonary fluid overload or pleural effusion. In case of reappearance (or increase) of pulmonary fluid overload or pleural effusion, fluid withdrawal is started again according to as described in paragraph 5.1.

5.2 Usual care/comparison

Routine fluid deresuscitation in which fluid withdrawal is started and continued at the discretion of the treating physician; Factors guiding fluid deresuscitation are chosen by the treating physician and may include the following: physical examination, laboratory values (e.g. BNP), CXR, PiCCO or pulmonary artery catheters. LUS examinations are not performed to guide fluid deresuscitation in this group.

5.3 General treatment of subjects

It is strongly suggested (a) to use protocolized sedation, using a sedation score with sedation targets at least 3 times a day, and preference for bolus sedation over continuous infusion of sedatives unless this is deemed impossible; (b) to use a weaning protocol

5.3.1 Weaning

The ventilator can be switched to partially supported ventilation mode at any moment the attending nurse or physician consider the patient respiratory drive is sufficient to breathe with partially supported ventilation.

At least once a day assessment of the ability to breathe without mechanical ventilation is required as soon as (1) $FiO_2 \leq 0.5$ or (2) when the PEEP level (≤ 10 cm H_2O) and FiO_2 level are lower than the day before[19].

A patient is assumed to be ready for extubation when the following criteria are met for at least 30 minutes:

- Responsive and cooperative;
- Adequate cough reflex;
- PaO_2/FiO_2 of > 200 mmHg with FiO_2 ≤ 50% and PEEP ≤10cmH2O;
- Respiratory rate of 8 to 30/minute with pressure support level < 10 cm H_2O;
- No signs of respiratory distress (i.e., marked accessory muscle use, abdominal paradox, diaphoresis, marked dyspnea);
- Hemodynamically stable (systolic blood pressure 80 to 160 mmHg and heart rate 40 to 130/min) and no uncontrolled arrhythmia with no or low dose vasopressors (norepinephrine ≤ 0,2 µg/kg/min);
- Temperature > 36.0^{o}C and < 38.5^{o}C.

If a patient becomes dyspneic/hypoxemic after extubation both non–invasive ventilation and high-flow nasal cannula are allowed as first line of therapy.

5.3.2 Tracheostomy

Early tracheostomy has no advantage over late tracheotomy[29]. Therefore, tracheostomy is only to be performed on strict indications and preferably not earlier than 10 days after intubation.

Strict indications for tracheostomy:

- Failure to intubate;
- 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;
- Prolonged or unsuccessful weaning;
- Repeated respiratory failure after extubation.

Weaning with a tracheostomy follows the rules as described above under ‘weaning’. A suggested scheme for unassisted ventilation with a tracheostomy is described in APPENDIX II.

5.3.3 Sedation

Sedation follows local guidelines for sedation in each participating units. 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) [30, 31]. 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. 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).

5.3.4 Selective oropharyngeal– or digestive tract decontamination

To prevent nosocomial infections, selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD) is performed in all patients who are expected to need ventilation for longer than 48 hours, and/or are expected to stay in ICU for longer than 72 hours.

5.3.5 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 extra–corporal circulation like veno–venous hemofiltration. Thrombosis prophylaxis will be given according to local guidelines.

5.3.6 Fluid regimens

In general, fluid therapy is targeted at adequate organ perfusion; e.g. a diuresis of ≥ 0.5 ml/kg/hour, well perfused skin without mottling. Crystalloid and balanced infusions are preferred over colloid infusions.

Occurrence of hypernatremia or atrial fibrillation during deresuscitation and fluid withdrawal in hemodynamically stable patients are treated as follow:

- Atrial fibrillation: continuation of fluid withdrawal is advised.

- Hypernatremia 145 – 155: continuation of fluid withdrawal is advised, consider administration of enteral free water and/or intravenous 5% dextrose solution. (target fluid balance remains unchanged)
- Hypernatremia above 155: discontinuation of fluid withdrawal and administration of enteral free water and/or intravenous 5% dextrose solution is advised. (target fluid balance 0 to slightly positive at discretion of treating physician)

5.3.7 Nutrition

Nutrition of each participant will follow standard European guidelines. A hypo–caloric, protein–rich diet (1.2–1.7 gr/kg bodyweight /24 hours) is started as soon as possible after ICU admission. Enteral nutrition with a feeding gastric tube is the preferred over intravenous feeding. If stomach retention occurs a duodenal tube can be used if administration of prokinetics is not sufficient, according to local guidelines. When optimal protein intake cannot be reached within 7 days, additional total parenteral nutrition (TPN) can be started[20].

6 STUDY PARAMETERS/ENDPOINT

6.1 Main study parameter/endpoint

The primary endpoint is the number of ventilator–free days and alive at day 28, defined as the number of days from day 1 to day 28; the patient is alive and breathes without assistance of the mechanical ventilator, if the period of unassisted breathing lasted at least 24 consecutive hours (APPENDIX II)

6.1.1 Secondary study parameters/endpoints

Secondary study parameters/endpoints include:

- Duration of invasive ventilation;
- 28-day mortality;
- ICU, Hospital, and 90-day mortality;
- ICU- and Hospital LOS;
- Cumulative fluid balance on day 1-7 after randomization;
- Cumulative fluid balance on day 1-7 after start of LUS examination;
- Mean serum lactate on day 1-7;
- Incidences of reintubations (not successful liberation (APPENDIX III));
- Incidences of chest drains;
- Incidences of atrial fibrillation (APPENDIX III);
- Incidences of kidney injury (KDIGO stadium ≥ 2 (APPENDIX III));
- Incidences of hypernatremia (serum sodium > 150 mmol/L);
- Use of invasive hemodynamic monitoring (PiCCO and pulmonary artery catheter);
- Use of chest-X-ray;
- Quality of life at day 28 (APPENDIX IV).

For follow-up after 28 and 90 days, with a visiting window of 2 weeks after day 28 and day 90, the patient will receive a phone-call when being discharged from the hospital in the previous period.

6.2 Randomization, blinding and treatment allocation

6.2.1 Screening

Patients in participating centers are screened during their first day of stay in the ICU and under invasive ventilation. Screened patients that do not meet the criteria or where informed consent is not obtained are excluded. Reason for exclusion are recorded for each screened patient.

6.2.2 Randomization

Patients will be randomly assigned in a 1:1 ratio to one of the following arms of the trial: LUS-guided fluid deresuscitation or routine fluid deresuscitation. To ensure allocation concealment, randomization sequence is generated by Castor EDC. Castor EDC is fully GCP and FDA compliant software. Randomization will be stratified by center. Randomization sequence will be blocked. Randomization will be performed using a dedicated, password protected, SSL-encrypted website. If possible, informed consent from the legal representative will be obtained before randomization but no longer than 48 hours after meeting the inclusion criteria.

6.2.3 Blinding

Inherently to the type of intervention blinding of the caregivers is not possible, as the intervention is used for guiding management. Data analysis, however, will be performed blinded for the study intervention.

6.3 Data collection

Data is collected using Castor EDC. Lung ultrasound observation scores are collected using LimeSurvey. Data collected on admission and within first 24 hours:

- Gender and age (male + years)
- Height and weight at admission (kg + cm)
- Relevant medical history
- Reason for ICU admission
- Reason for ventilation
- Cause of respiratory failure
- APACHE II score and SAPS II score

- Respiratory status, on admission, and every day until day :
  - Intubation status (if extubated: time of extubation)
    - If reintubated: specify reason why
  - Tracheostomy status (if tracheostomized: time of tracheostomy)
  - Invasiveness of ventilation (invasive, non–invasive, or intermittent ventilation via tracheostomy, use of HFNO)
- Every day at a fixed time point until day 28, and at day 90:
  - Location of patient, (in ICU, hospital, other facility, or home) and
  - Life status (alive or deceased)
- Every day until day 28 or discharge from ICU, whatever comes first:
  - Use of pulmonary artery catheter and or PiCCO (yes or no),
  - Use of chest-X-ray and or chest-CT (yes or no)
  - Atrial fibrillation (yes or no) (APPENDIX III)
  - Acute kidney injury (yes or no) (APPENDIX III)
  - ARDS (yes or no) (APPENDIX III)
- Twice daily until day 28 or discharge from ICU, whatever comes first:
  - For intervention group: use of lung ultrasound (yes or no)
    - If yes: lung ultrasound score (APPENDIX I)
    - If not: specify reason why
  - For control group: use of lung ultrasound (yes or no)
    - If yes: specify reason why
- At day 28:
  - Quality of life (APPENDIX IV)

6.4 Other data to be collected

- Mechanical ventilation parameters every day until day 7 at a fixed time point
  - Tidal volume (ml + ml/kg PBW)
  - Respiratory rate (breath/minute)
  - Level of positive end–expiratory pressure (cmH_2O)
  - Peak and plateau pressures, or level of pressure support (level above PEEP, and maximal airway pressure, cmH_2O)
  - Inspiration to expiration ratio
  - Inspired oxygen fraction (%)

  - Minute volume (liters/minute)
  - Pulmonary compliance (ml/ cmH_2O)
- Respiratory parameters every day at a fixed time point until cessation of ventilation:
  - Peripheral oxygen saturation (%)
  - End–tidal fractions of CO2 (kPa)
  - PaO2 (kPa)
  - PaCO2 (kPa)
  - Arterial bicarbonate (mmol/L)
  - Arterial pH
  - Arterial base excess (mmol/L)
- Clinical data, every day until day 28 or discharge from ICU, whatever comes first:
  - Vital signs (heartrate and blood pressure)
  - Glasgow Coma Scale (GCS)
  - Transfusions of blood products (type and ml)
  - Infusion of crystalloids (type and ml)
  - Infusion of (artificial) colloids (type and ml)
  - Infusion of noradrenaline (mg)
  - Cumulative use of diuretics (type and mg)
  - Cumulative fluid balance (ml)
  - Cumulative urine output (ml)
  - Days on Renal Replacement Therapy (RRT)
  - Arterial lactate (mmol/L)
  - Creatinine (umol/L)
  - Urea (mmol/L)
  - Sodium (mmol/L)
  - Trombocytes ($x10^9$/L)
- Sequential Organ Failure Assessment score (SOFA) score (APPENDIX III)

6.5 Withdrawal of individual subjects

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

6.6 Follow-up of subjects withdrawn from treatment

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

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

Since we compare two strategies that are currently widely used in routine care, additional risks are not expected. 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 is 33%[17]). Therefore, we propose to report the secondary endpoints of this trial 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 safety endpoints (see below). These endpoints will be specified per study arm in the line listing without disclosing the specific arms.
The specific safety endpoints include:

- ICU mortality
- Incidence of acute kidney injury for which RRT is started (APPENDIX III)

7.3 Adverse events (AE) and Serious Adverse Events (SAE)

7.3.1 Adverse Events

Adverse events (AE) are defined as undesirable experience occurring to a subject during the study, whether or not considered related to the treatment.
All included patients are admitted to the Intensive Care with a life-threatening disease. Any adverse development can be expected as part of the underlying disease. Therefore, it is not achievable to report all these developments individually as AEs.

7.3.2 Serious adverse events

All included patients are admitted to the Intensive Care with a life-threatening disease. Any major adverse development can be expected as part of the underlying disease. Therefore, it is not achievable to report all these developments individually as SAEs. A list of SAEs mentioned below of all included patients is sent every 6 months to the medical ethics committee (METC) and DSMB.
If any other unexpected (serious) adverse events occur that might be related to the study intervention, these will also be reported to the METC and DSMB.

Events that can be considered SAEs within the context of this study population are:

- Death;
- Renal Replacement Therapy.

SAEs will be collected until 28 days after inclusion.

When included patients are transferred to another hospital within 28 days after inclusion, SAEs will be collected until moment of transfer.

7.4 Data Safety Monitoring Board (DSMB) / Safety Committee

The DSMB will be composed of 4 individuals, consisting of three renowned, independent intensivists and one statistician, one of which will be the chairman.

- The DSMB will first meet approximately 6-8 months after the first patient is enrolled; the first meeting will be scheduled after the first 150 patients.
- Subsequent to this meeting the DSMB will meet virtually every 6 months.
- The DSMB will monitor safety by monitoring the specific safety endpoints as described above.
- The DSMB will monitor protocol compliance of both treatment strategies by monitoring the use of lung ultrasound.
- 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 report and/ or advice(s) of the DSMB will only be sent to the sponsor of the study, Amsterdam University Medical Centers, location ‘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. We will also perform a per–protocol analysis, comparing patients who received LUS guided fluid deresuscitation and patients who received routine care. Other secondary analyses include analysis of patients who fulfilled the definition for ARDS versus patients who did not fulfill this definition, and patients with sepsis versus patients without sepsis.

8.2 Primary study parameter(s)

The goal of the primary analysis is to quantify the effect of LUS guided deresuscitation strategy vs. routine care on the number of ventilator free days and alive at day 28. The primary outcome, the number of ventilator–free days and alive at day 28 after ICU admission, is analyzed using an appropriate nonparametric analysis method to evaluate the confidence interval for the difference between the two medians of the ventilator–free days from both groups. Additionally, time to freedom from mechanical ventilation are expressed with Kaplan–Meier curves. Differences between both groups will be analyzed using the log–rank test.

8.3 Secondary study parameter(s)

Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as n (%). To test groups Student’s t test will be used, if continuous data is not normally distributed the Mann-Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher’s exact tests. Time dependent secondary endpoints will be analyzed using a proportional hazard model adjusted for possible imbalances of patient’s baseline characteristics. Analysis will be performed with R statistics version 3.0.2. Patient characteristics will be compared and described by appropriate statistics.

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

9.2.1 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 because of the following reasons.

Resuscitation and deresuscitation are one of the most often applied therapies in the ICU. Patients who are in shock and/or respiratory distress are in an emergency situation and need immediate medical support, start of resuscitation but also, when applicable, start of deresuscitation cannot be postponed. Patients admitted to an ICU are, without exception, not able to give informed consent. People 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 the ICU or when the patient meets the inclusion criteria. Obtaining informed consent from a legal representative takes time, even by an experienced research team, as consent requires sufficient time to read and consider the provided written information[21]. Furthermore, shortly after admission to the ICU and meeting the inclusion criteria, the legal representative are more concerned about the wellbeing of the patient then participation in a trial[22].

We propose to randomize each patient who meets the inclusion criteria ultimately within 24 hours after fulfilling the inclusion criteria. Deresuscitation according to randomization is started immediately thenceforth. Informed consent from the legal

representative will be requested as soon as possible, but never later than 48 hours after meeting the inclusion criteria. If possible informed consent from the legal representative will be obtained before randomization.

If informed consent from the legal representative is not obtained within those 48 hours, or if a legal representative denies participation within this time frame, the patient is excluded and data will no longer be used. Thenceforth the patient is treated according to the policy of the attending physician.

The representative will be given oral and written information in person or by telephone and email. Considering the recent Corona pandemic with limited visiting hours in the hospital and restricted travel options, written informed consent can also be given through email by legal representative within 12 hours after information is given, but no longer than 48 hours after meeting the inclusion criteria. At the shortest notice as possible, at least within 48 hours after obtaining written consent received by email, consent has to be confirmed written on paper[23].

A second informed consent is asked from the patient in retrospect, at the moment the patient is awake and able to judge about his or her situation properly. Information on the study is then provided and written informed consent is asked and signed by both the executive investigator and the patient. If a patient declines consent, all collected study data on this patient will be destroyed.

9.3 Benefits and risks assessment, group relatedness

We can underpin the idea of clinical equipoise. Burden and risks of the two deresuscitation strategies are uncertain. Both strategies are currently used in The Netherlands and worldwide; there is no additional risk for patients enrolled in this study compared to routine care.

We specifically chose *not* to exclude incompetent patients for two reasons. First, most if not all severely ill patients needing mechanical ventilation should be considered incompetent due to their needs for continuous sedation. Second, the strategies to be compared in this study are to be used in severely ill, intubated and ventilated patients. These conditions are not present in patients who are not suffering from a critical disease. We therefore consider it impossible not to include these patients in a study

comparing strategies for treating mechanical ventilated patients to be used in that specific patient group.

9.4 Compensation for injury

The sponsor/investigator has a liability insurance, which is in accordance with article 7 subsection 6 of the WMO. As this study has no additional risks for patients an exemption from the requirement to insure cover for damage to research subjects through injury or death caused by the study is applicable, in accordance with article 7, subsection 5 of the WMO.

10 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All patients will be addressed to with a random patient identification code. The codebook will be stored digitally and in paper. 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, for further publication. All handling of personal data will comply with the Dutch Personal Data Protection Act. The principal investigator, coordinating investigators, healthcare inspectorate (IGJ) monitors and auditors will have access to the data and documents.

10.2 Monitoring and Quality Assurance

The objective of the clinical data management plan is to provide high–quality data by adopting standardized procedures to minimize the number of errors and missing data, and consequently, to generate an accurate database for analysis. Accuracy and consistency checks will be carried out by way of automatic validation, pre-specified and ad hoc checking by personnel at the coordinating centers.

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 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.

10.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

10.4 Annual progress report

The sponsor/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, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 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. In case the study is ended prematurely, the investigator 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.

10.6 Public disclosure and publication policy

The study protocol and analysis plan will be published before start of the study 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 as well as anesthesiology, since both ICU physicians and anesthesiologists treat these patients in the ICU setting.

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APPENDIX I: LUNG ULTRASOUND EXAMINATION

Lung ultrasound is performed for 12-regions to assess the lung. Each chest wall can be divided in to six lung regions: upper and lower parts of the anterior, lateral and posterior chest wall as can be seen in the figure below.

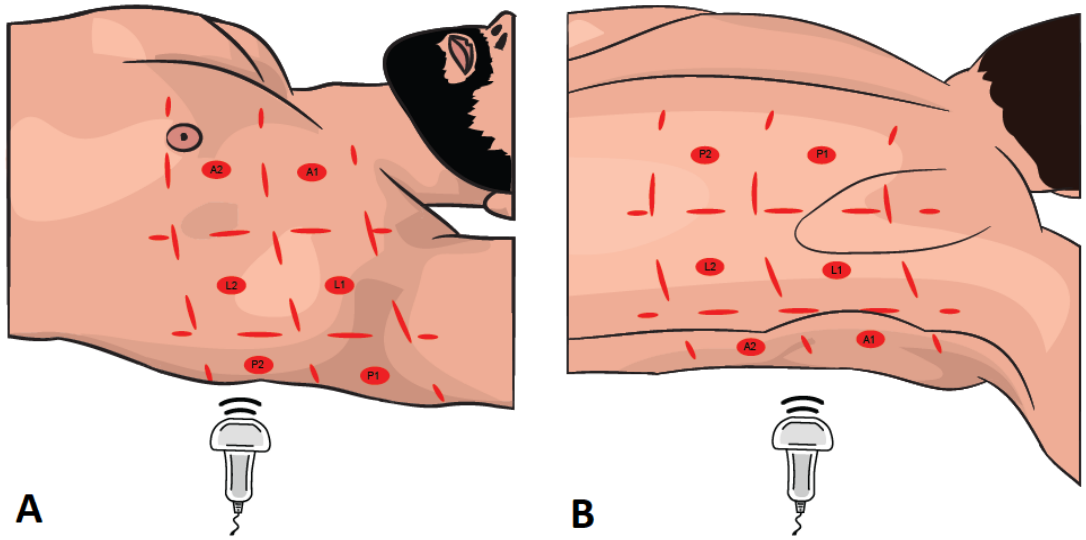


Figure 2: Lung regions used for lung ultrasound examination. A. supine position. Each hemithorax is divided in to six regions: upper and lower parts of the anterior, lateral and posterior chest wall. B: prone position. Each hemithorax is divided in to six regions: upper and lower parts of the posterior, lateral and anterior chest wall.

For each lung region, points are allocated according to the worst ultrasound pattern observed:

- A-profile (0 points): No loss of lung aeration and presence of lung sliding with A-lines or <3 isolated B-lines;
- B1-profile (1 point): Moderate loss of lung aeration: ≥3 well defined B lines or <50 % of pleural surface affected;
- B2-profile (2 points): Severe loss of lung aeration: multiple coalescent B lines or ≥50 % of pleural surface affected;
- C-profile (3 points): Complete loss of lung aeration

Significant pleural effusion: >1 cm of pleural effusion in lateral regions and/or >2 cm of pleural effusion in posterior regions.

The lung ultrasound score is calculated as the sum of points of each lung region.

APPENDIX II: 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 III: DEFINITIONS

- ARDS (Acute Respiratory Distress Syndrome): is defined by the characteristics according to the 2012 Berlin definition:
    - Timing: Within 1 week of a known clinical insult, or new/worsening respiratory symptoms; and
    - Chest imaging (chest radiograph or chest-CT): Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules; and
    - 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; and
    - Oxygenation
        - Mild: 200 < PaO2/ FiO2 ≤ 300 mmHg (26.7 < PaO2/ FiO2 ≤ 40 kPa) with PEEP ≥ 5 cm H2O or CPAP ≥ 5 cm H2O
        - Moderate: 100 < PaO2/ FiO2 ≤ 200 mmHg (13.3 < PaO2/ FiO2 ≤ 26.7 kPa) with PEEP ≥ 5 cm H2O
        - Severe: PaO2/ FiO2 ≤100 mmHg (PaO2/ FiO2 ≤ 13.3 kPa) with PEEP ≥ 5 cm H2O
- Atrial Fibrillation: a cardiac arrhythmia with the following electrocardiographic characteristics:
    - No discrete P-waves; and
    - Fibrillatory or F-waves present at rates of 350 to 600 beats/min (or unmeasurable); the f waves vary continuously in amplitude, morphology, and intervals; and
    - The RR intervals are irregularly irregular.
- APACHE (Acute Physiology and Chronic Health Evaluation) II: a point score ranging from 0–71, calculated from 12 measurements (age, temperature (rectal), mean arterial pressure, pH, heart rate, respiratory rate, sodium (serum), potassium (serum), creatinine, hematocrit, white blood cell count, Glasgow Coma Scale) higher scores correspond to more severe disease and higher risk of death.
- KDIGO Acute Kidney Injury: is defined as any of the following:
    - An increase of serum creatinine by ≥ 0.3 mg/dl or 26.5 µmol/L within 48 hours; or

- An increase of serum creatinine by ≥ 1.5 times baseline which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 ml/kg/h for 6 hours.

Stage	Serum creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase	< 0.5 ml/kg/h for 6-12 hours
2	2.0 – 2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase to ≥ 4.0 mg/dl (≥ 353.6 µmol/l) OR Initiation of renal replacement therapy	< 0.3 ml/kg/h for ≥ 24 hours OR anuria for ≥ 12 hours

- Reintubation: intubation within the next 72 hours after extubation (planned or unplanned)
- SAPS (Simplified Acute Physiology Score) II: point score ranging from 0–163, as APACHE.
- SOFA (Sequential Organ Failure Assessment): a point score ranging from 4–4, calculated from 6 measurements (PaO_2/FiO_2 ratio, Glasgow Coma Scale, Mean Arterial Pressure (MAP), bilirubin, platelets and creatinine) higher scores correspond to more severe disease and higher risk of death.
- VFD-28 (Ventilator-free days and alive at day 28):
  - VFD–28 = 0 if subject dies within 28 days of mechanical ventilation
  - VFD–28 = 28 – x if successfully liberated from ventilation x days after initiation
    - Successful liberation: extubation (planned or unplanned) without death or reintubation within the next 72 hours
  - VFD–28 = 0 if the subject is mechanically ventilated for ≥ 28 days

APPENDIX IV: EQ- 5D-5L QUALITY OF LIFE QUESTIONNAIRE

English version:

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

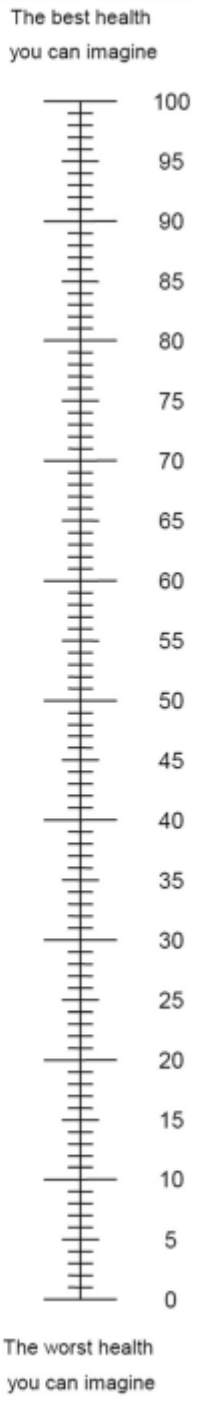
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discom ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Dutch version:

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

Ik heb geen problemen met lopen ❑
Ik heb een beetje problemen met lopen ❑
Ik heb matige problemen met lopen ❑
Ik heb ernstige problemen met lopen ❑
Ik ben niet in staat om te lopen ❑

ZELFZORG

Ik heb geen problemen met mijzelf wassen of aankleden ❑
Ik heb een beetje problemen met mijzelf wassen of aankleden ❑
Ik heb matige problemen met mijzelf wassen of aankleden ❑
Ik heb ernstige problemen met mijzelf wassen of aankleden ❑
Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
Ik heb matige problemen met mijn dagelijkse activiteiten ❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN/ONGEMAK

Ik heb geen pijn of ongemak ❑
Ik heb een beetje pijn of ongemak ❑
Ik heb matige pijn of ongemak ❑
Ik heb ernstige pijn of ongemak ❑
Ik heb extreme pijn of ongemak ❑

ANGST/SOMBERHEID

Ik ben niet angstig of somber ❑
Ik ben een beetje angstig of somber ❑
Ik ben matig angstig of somber ❑
Ik ben erg angstig of somber ❑
Ik ben extreem angstig of somber ❑

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de beste gezondheid die u zich kunt voorstellen.
  0 staat voor de slechtste gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐