Statistical Analysis Plan of the ‘Effect of lung Ultrasound–guided Fluid Deresuscitation on Duration of ventilation in Intensive Care unit patients’ trial (CONFIDENCE)

The CONFIDENCE–investigators

INTRODUCTION

The ‘Effect of lung Ultrasound–guided Fluid Deresuscitation on Duration of ventilation in Intensive Care unit patients’ trial (CONFIDENCE) compares a fluid deresuscitation strategy guided by repeated lung ultrasound (LUS) to usual care in intensive care unit (ICU) patients receiving mechanical ventilation [1]. The primary objective of this study is to determine whether LUS–guided fluid deresuscitation strategy (‘LUS-guided’ group) is superior to usual care (‘usual care’ group) with regard to the number of ventilator–free days and alive at day 28. Enrollment of patients in CONFIDENCE already started and the study is planned to finish around the third trimester of 2025.

To prevent outcome reporting bias and data–driven analysis results, the International Conference on Harmonization of Good Clinical Practice (ICH–GCP) recommends that clinical trials should be analyzed according to a pre–specified detailed Statistical Analysis Plan (SAP). This document presents the updated and finalized SAP of CONFIDENCE.

METHODS

Design

The protocol, with a detailed description of the study population, the two interventions and follow–up plan of CONFIDENCE was published before [1]. CONFIDENCE is registered in clinicaltrials.gov (study identifier NCT05188092) and is approved by the Institutional Review Board of the Amsterdam University Medical Centers, location Academic Medical Center, in Amsterdam, The Netherlands (2021_182). CONFIDENCE is an investigator–initiated, international, multicenter, parallel two–arm randomized clinical superiority trial, comparing a LUS–guided fluid deresuscitation strategy ('LUS-guided' group) with usual care ('usual care' group) in ICU patients receiving mechanical ventilation.

Randomization and blinding

Eligible patients are randomly allocated in a 1:1 ratio to the 'LUS-guided' or the 'usual care' strategy. The allocation sequence is computer–generated by an independent investigator using permuted blocks of different block sizes, with a maximum block size of ten and stratified by center. Randomization is performed by local investigators patient–by–patient employing a dedicated, password protected, SSL–encrypted website. Due to the nature of the intervention tested, blinding is not possible.

Outcomes

The primary outcome is the number of ventilator–free days and alive at day 28, defined as the number of days from day 1 to day 28 when the patient is alive and breathes without invasive assistance of the mechanical ventilator for at least 24 consecutive hours. To calculate this endpoint all relevant data will be taken into account and collected, including all additional periods of ventilation during the first

28 days. In case of multiple extubations within day 28, only the last extubation will be considered for this endpoint. Patients who die before day 28 or are invasively ventilated for longer than 28 days are assigned to have zero ventilator–free days. The complete definition, as suggested [2], is shown in **Table 1**.

Secondary outcomes include (definition are described in **Table 1**):

- Duration of ventilation in survivors;
- Cumulative fluid balance on days 1-7 after randomization;
- Cumulative fluid balance on days 1-7 after start of LUS examination;
- Mean serum lactate on days 1-7 after randomization;
- Incidence of reintubation;
- Chest drain placement during ICU admission;
- Incidence of atrial fibrillation during ICU admission;
- Incidence of acute kidney injury (AKI) Kidney Disease Improving Global Outcomes (KDIGO) stage ≥ 2 [3] during ICU admission;
- Incidence of hypernatremia (defined as sodium > 150 mmol/L) during ICU admission;
- Use of invasive hemodynamic monitoring during ICU admission;
- Chest X-ray performed during ICU admission;
- Chest CT performed during ICU admission;
- Quality of life in survivors at day 28 (assessed using EuroQol five-dimension, five-level questionnaire [EQ-5D-5L] [4]);
- ICU length of stay;
- Hospital length of stay;
- ICU mortality;
- Hospital mortality;

- 28–day mortality; and
- 90–day mortality.

Cleaning and closing of the database

The database will be locked as soon as all data are entered and all discrepant or missing data are resolved, after all efforts are employed to complete the database, and we consider that the remaining issues cannot be fixed. At this step, the data will be reviewed before database locking. After that, the study database will be locked and exported for the statistical analysis. At this stage, permission for access to the database will be removed for all investigators, and the database is locked and archived.

Missing data

No or minimal losses to follow–up for the primary outcome is anticipated. Complete–case analysis will be carried out for all the outcomes. However, if more than 5% of missing data is found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out. Multiple imputation will consider imputation models based on prognostic baseline and post-baseline variables under a missing at random assumption.

Sample size

The trial was designed to last until 1000 patients are enrolled. This number of patients was expected to be sufficient to show superiority of the ‘LUS-guided’ versus the ‘usual care’ strategy considering a difference of 2.0 in ventilator–free days at day 28, assuming a mean and common standard deviation of 17 and 11, respectively [5,6], a two–sided alpha level of 5%, 80% of power, similar allocation of subjects to each group and corrected for 5% of dropouts.

Statistical analyses

All statistical analyses will be conducted on an intention–to–treat basis, with patients analysed according to their assigned treatment arms, except for cases lost to follow up or withdrawal of informed consent. In addition, a per–protocol analysis will be conducted. All analyses will be performed using a common two–sided superiority hypothesis test, with a significance level of 0.05 and presented with two–sided 95% confidence intervals. In addition to the unadjusted *p* values for secondary outcomes, a Holm–Bonferroni procedure will be applied to control for multiple testing [7]. Analyses will be performed using the software R (R Core Team, 2016, Vienna, Austria). A list of proposed tables and figures is in **Table 2**.

Trial profile

Patient flows will be represented in a CONSORT flowchart (**Figure 1**)**.**

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group (**Table 3**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be summarized by either means and standard deviations (±SD) or medians and interquartile ranges (IQR), according to the observed distribution of the variable.

The fluid deresuscitation strategies

Protocol compliance will be assessed as the daily use of LUS in the LUS-guided deresuscitation group over the first 10 days after randomization and the difference in fluid balance and other hemodynamic variables among the groups from the pre–randomization until day 10 will be shown in line plots and compared

using mixed–effect longitudinal models with patients and centers as random effect, the variable of interest as the dependent variable and the moment of measurement, randomization group and an interaction of day and randomization group as fixed effects. Two *p* values will be reported: 1) *p* value for the group difference, reflecting the overall test for difference between groups across the five days; and 2) *p* values for the group x day interaction, evaluating if change over time differed by group. In addition, since it is expected that the baseline values will be similar between the groups, these will be exposed in the graphs but excluded from the models.

Other daily characteristics

Daily variables, including sedation, transfusion, fluid therapy and use of vasoactive drugs will be reported according to the description in **Table 2**. Absolute differences between the groups with the respective 95% confidence interval will be calculated as mean differences from a mixed–effect linear model considering the centers as random effect to account for within–center clustering in continuous variables and as absolute differences derived from a generalized linear model considering a binomial distribution with an identity-link and with centers as random effect to account for within–center clustering for categorical variables. Models will include an interaction term between randomization group and time (as a continuous variable).

Primary outcome

The effect of 'LUS-guided' compared to 'usual care' deresuscitation strategy on the ventilator–free days at day 28 will be presented as a odds ratio, and presented as a two–sided 95% confidence interval calculated from a mixed-effect cumulative logistic model considering the centers as random effect to account for

within–center clustering. Cumulative logistic models consider the ranking and ordinal structure of ventilator-free days. In this model, the cumulative log odds is modeled such that a parameter greater than 0 reflects an increase in the cumulative odds for the ventilator-free days outcome, which implies benefit. A potential advantage of this model is that, with multinomial sampling of independent subjects, the score test statistic from the model is similar to the Wilcoxon rank-sum test statistic [8], one of the most powerful tests to analyze ventilator-free days in a variety of scenarios [2]. This approach is being consistently used in trials in the critical care field [9,10]. To increase transparency, the data will be presented by group also as means (± SD). Results will be presented in a table of outcomes (**Table 4**). A cumulative incidence plot will be used to plot the distribution of the outcome by group and with non-survivors coded as -1.

Secondary outcomes

The effect of the intervention on binary outcomes will be assessed with absolute differences derived from a generalized linear model considering a binomial distribution with an identity-link and with centers as random effect to account for within–center clustering. The duration of ventilation in survivors, cumulative fluid balance, mean serum lactate levels, and the ICU– and hospital length of stay will be assessed with median difference from a mixed-effect median regression with centers as clustering effect. 28– and 90–day mortality will be compared using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with (shared-frailty) Cox proportional hazard models with center included as frailty. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality

assumption is not sustained. In addition, a Holm–Bonferroni correction to control the family–wide error rate to the *p* values for all 18 secondary outcomes will be done and presented in a Table.

Per–protocol analysis

The per–protocol analysis only considers those patients who were treated according to the originally allocated treatment study protocol. Patients will be included in the per-protocol population if both of the following criteria are met: 1) hemodynamic stabilization, defined as at least one study day during ICU admission meeting all of the following: a) serum lactate < 2.5 mmol/L; and b) no norepinephrine given or total daily dose < 0.2 µg/kg/min per kg of admission body weight; and 2) protocol adherence by treatment group, defined as: a) intervention group: at least one lung ultrasound performed according to the study protocol; and b) control group: no lung ultrasound performed for fluid status monitoring during the study period, but diagnostic ultrasound for acute indications are allowed.

Additional analysis

As additional analyses, the effect of the intervention on primary and secondary outcomes will be re–estimated using mixed–effect models incorporating adjustment for age, gender, prognostic score as well as for any observed baseline differences. These models will incorporate the underlying distribution of each outcome as described above.

Subgroup analysis

The homogeneity of treatment effects on the primary outcome across subgroups will be examined via a test for treatment–by–subgroup interaction in the cumulative logistic model irrespective of whether there is evidence of a treatment

effect. Results will be summarized by subgroup and presented as common odds ratio with two–sided 95% confidence intervals. Lack of a significant interaction will imply that the results are consistent across subgroups and that the overall effect estimated are the most appropriate estimates of treatment effect within each subgroup. The results will be presented in a forest plot with a solid line of reference in the number 1 and a dashed line of reference in the overall effect. The following subgroups at randomization will be assessed:

- Age (≤ 65 or > 65 years);
- Sex (male or female);
- Body mass index (< 30 or ≥ 30 kg/m^2);
- SOFA (< median or ≥ median);
- Reason of ICU admission (medical or surgical);
- Reason for intubation (respiratory or non-respiratory);
- Hours between ICU admission and randomization (< median or ≥ median);
- Hypoxemic respiratory failure (yes or no);
- Sepsis (yes or no);
- Cardiac arrest (yes or no);
- Chronic kidney disease (yes or no);
- Acute kidney injury (yes or no);
- Renal replacement therapy (yes or no).

SUMMARY

CONFIDENCE is an investigator–initiated, national, multicenter parallel two–arm randomized clinical superiority trial. This trial is comparing a LUS-guided fluid deresuscitation strategy with a usual care strategy in 1000 adults who are expected to need invasive ventilation beyond the first 24 hours. The primary outcome is ventilator–free days and alive at day 28. The here reported SAP was updated and finalized before completion of enrollment.

REFERENCES

1. Blok SG, Mousa A, Brouwer MG, et al. Effect of lung ultrasound-guided fluid deresuscitation on duration of ventilation in intensive care unit patients (CONFIDENCE): protocol for a multicentre randomised controlled trial. Trials 2023;24:226-36.

2. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Re-appraisal of ventilator-free days in critical care research. Am J Respir Crit Care Med 2019;[in press].

3. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179–c184.

4. Gerth AMJ, Hatch RA, Young JD, Watkinson PJ. Changes in health related quality of life after discharge from an intensive care unit: a systematic review. Anaesthesia 2019;74:100–08.

5. Writing Group for the PReVENT Investigators, Simonis FD, Serpa Neto A, et al. Effect of a Low vs Intermediate Tidal Volume Strategy on Ventilator-Free Days in Intensive Care Unit Patients Without ARDS: A Randomized Clinical Trial. JAMA 2018; 320:1872-80.

6. van Meenen DMP, van der Hoeven SM, Binnekade JM, et al. Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation: A Randomized Clinical Trial. JAMA 2018; 319:993-1001.

7. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979; 6:65-70.

8. Natarajan S, Lipsitz SR, Fitzmaurice GM, et al. An extension of the Wilcoxon Rank-Sum test for complex sample survey data. J R Stat Soc Ser C Appl Stat 2012; 61:653-64.

9. Angus DC, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA 2020; 324:1317-29.

10. The REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med 2021; 384:1491-502.

Table 1 – Definitions of outcomes

Outcomes	Definition
Ventilator–free days at day 28	Start time: day of randomization. Timeframe: 28 days. Successful extubation: > 24 hours without reintubation in a 28–day survivor. Interval reintubation: counted from the day of the last successful extubation if there were repeated intubation episodes in the first 28 days. Non–invasive ventilation: not counted. Tracheostomy: same as above (> 24 hours off positive pressure ventilation). 28–day non–survivors: 0 ventilator–free days even if extubated in the period. Death after 28 days: censored and considered the duration of ventilation only.
Duration of ventilation in survivors	Duration, in days, between intubation and successfully extubation, defined as a patient breathing without invasive assistance of the mechanical ventilator for at least 24 consecutive hours. All relevant data will be taken into account and collected, including all additional periods of ventilation during the first 28 days. Only patients surviving the first 28 days will be considered.
Cumulative fluid balance on days 1-7 after randomization	Defined as the sum of all daily fluid balances from day 1 until day 7 after randomization.
Cumulative fluid balance on days 1-7 after start of LUS examination	Defined as the sum of all daily fluid balances from day 1 until day 7 after start of LUS examination.
Mean serum lactate on days 1-7 after randomization	Defined as the mean lactate level considering all lactate levels measured from day 1 until day 7 after randomization.
Incidence of reintubation	Defined as any reintubation within the next 72 hours after extubation (planned or unplanned).
Chest drain placement	Defined as the placement of a chest drain (for any indication) as indicated by the treating physician during ICU stay.
Incidence of atrial fibrillation	Defined as a cardiac arrhythmia with the following electrocardiographic characteristics during ICU stay: • 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.
Incidence of acute kidney injury	Acute kidney injury based on Kidney Disease Improving Global Outcomes (KDIGO) stage ≥ 1 defined as [3] during ICU stay: • Serum creatinine ≥ 2.0 times baseline; OR • Increase of serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 µmol/L); OR • Urine output < 0.5 mL/kg/h for ≥ 12 hours; OR • Urine output < 0.3 mL/kg /h for ≥ 24 hours; OR • Anuria for ≥ 12 hours; OR • Initiation of renal replacement therapy.
Incidence of hypernatremia	Defined as a serum sodium level > 150 mmol/L during ICU stay.
Use of invasive hemodynamic monitoring	Defined as the placement of a Swan-Ganz or Pulse index Continuous Cardiac Output Catheter during ICU admission.

Chest X-ray	Defined as the use of a chest X-ray for any indication during ICU admission.
Chest computerized tomography	Defined as the use of a chest computerized tomography for any indication during ICU admission.
Quality of life in survivors at day 28	Assessed using EuroQol five-dimension, five-level questionnaire [EQ-5D-5L] [4]
ICU length of stay	Number of days from randomization till ICU discharge. Counted from the day of the last ICU discharge if there were repeated readmissions.
Hospital length of stay	Number of days from randomization till hospital discharge.
ICU mortality	Any death occurring during ICU stay.
Hospital mortality	Any death occurring during hospital stay.
28–day mortality	Any death occurring during the first 28 days after randomization.
90–day mortality	Any death occurring during the first 90 days after randomization.

Abbreviations: LUS is lung ultrasound.

Table 2 – List of proposed tables and figures

	Description
Main paper	
Table 1	Baseline Characteristics
Table 2	Primary and Secondary Outcomes
Figure 1	Daily and Cumulative Fluid Balance Over the First Ten Days After Randomization *Line plot reporting A) daily fluid balance, and B) cumulative fluid balance according to randomization group. Mean and 95% confidence intervals will be reported.*
Figure 2	Clinical outcomes for patients in the LUS-guided and usual care groups *A four panels figure showing: A) Cumulative distribution of ventilator-free days at day 28 in a cumulative proportion for each study group by day; B) Ventilator-free days at day 28 as horizontally stacked proportions by study group; C) Kaplan–Meier curve for the 28–day survival in both groups; and D) Kaplan–Meier curve for the 90–day survival in both groups.* *For panel C and D a hazard ratio and 95% confidence interval calculated from a (shared-frailty) Cox proportional hazard model will be presented.*
Figure 3	Subgroup analysis *A forest plot showing the common odds ratio and two–sided 95% confidence intervals with p value for interaction calculated via a test for treatment–by–subgroup interaction in the cumulative logistic model. A solid line of reference in the number 1 and a dashed line of reference in the overall effect will be shown.*
Online Supplement	
eTable 1	Additional Baseline Characteristics
eTable 2	Additional Characteristics on the First Day of Randomization
eTable 3	Laboratory Tests and Ventilation Data on the First Day of Randomization
eTable 4	Lung Ultrasound Results on the First Day of Hemodynamic Stabilization
eTable 5	Fluid Balance Over the First Ten Days After Randomization
eTable 6	Fluid Intake, Output and Balance Over the First Ten Days After Randomization
eTable 7	Sequential Organ Failure Assessment Over the First Ten Days After Randomization
eTable 8	Use and Dose of Vasopressor Over the First Ten Days After Randomization
eTable 9	Laboratory Tests Over the First Ten Days After Randomization
eTable 10	Ventilation Variables Over the First Ten Days After Randomization
eTable 11	Additional Outcomes
eFigure 1	Management of Patients According to the Allocated Arm
eFigure 2	Participant Flow Diagram
eFigure 3	Protocol Compliance Over the First Ten Days After Randomization *Line plot reporting protocol compliance on the LUS-guided group. Mean and 95% confidence intervals will be reported.*
eFigure 4	Daily SOFA Over the First Ten Days After Randomization *Line plot reporting A) total SOFA, B) cardiovascular SOFA, C) respiratory SOFA, and D) renal SOFA according to randomization group. Mean and 95% confidence intervals will be reported.*
eFigure 5	Daily Vasopressor Use Over the First Ten Days After Randomization *Line plot reporting A) percentage of patients using vasopressor, and B) vasopressor dose (in noradrenaline equivalents) according to randomization group. Mean and 95% confidence intervals will be reported.*
eFigure 6	Daily Laboratory Tests Over the First Ten Days After Randomization *Line plot reporting A) lactate, B) creatinine, C) sodium, and D) chloride according to randomization group. Mean and 95% confidence intervals will be reported.*

eFigure 7 Daily Ventilation Variables Over the First Ten Days After Randomization

Line plot reporting A) tidal volume per PBW, B) PEEP, C) peak pressure, D) plateau pressure according to randomization group. Mean and 95% confidence intervals will be reported.

Table 3 – Baseline Characteristics

	LUS-guided (*n* =)	Usual Care (*n* =)
Age, years		
Female sex		
BMI, kg/m^2		
Days between hospital and ICU admission		
Days between ICU admission and randomization		
Hours between intubation and randomization		
Prognostic score		
APACHE III		
SAPS II score		
Sepsis – no. (%)		
Cardiac arrest – no. (%)		
Hypoxemic respiratory failure* – no. (%)		
Premorbid creatinine**, µmol/L		
Reason of ICU admission – no. (%)		
Planned surgery		
Emergency surgery		
Medical		
Other		
Reason of intubation – no. (%)		
Respiratory		
Non-respiratory		
Co-existing disorders – no. (%)		
Atrial fibrillation		
Chronic kidney disease		
Heart failure		
Chronic obstructive pulmonary disease		
On the day of randomization		
SOFA		
Acute kidney injury – no. (%)		
Received renal replacement therapy – no. (%)		
Use of vasopressor – no. (%)		
Blood transfusion – no. (%)		
Use of diuretics – no. (%)		
Total fluid balance, mL		
Lactate, mmol/L		
PaO_2 / FiO_2		
Ventilation data		
Tidal volume, mL/kg predicted body weight		
PEEP, cmH_2O		
Peak pressure, cmH_2O		
Plateau pressure, cmH_2O		
FiO_2, %		

Data are median (quartile 25^{th} – quartile 75^{th}) or number (percentage).

Abbreviations: LUS is lung ultrasound; BMI is body mass index; SAPS is Simplified Acute Physiology Score; APACHE is Acute Physiology and Chronic Health Evaluation; ICU is intensive care unit; PEEP is positive end-expiratory pressure; SOFA is Sequential Organ Failure Assessment.

* Defined as a PaO_2 / FiO_2 < 300 on the day of randomisation and a respiratory reason for intubation.

** Premorbid creatinine hierarchically defined as follows: 1) the lowest available creatinine level between 1 year before admission and 24 hours before hospital admission; or 2) the lowest creatinine level between 24 hours before hospital admission and admission to the intensive care unit; or 3) the creatinine level was estimated using the formula: creatinine = 88.4 x 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years).

Table 4 – Primary and Secondary Outcomes

	LUS-guided (*n* =)	Usual Care (*n* =)	Effect Estimate (95% CI)	*p* value
Primary outcome				
Ventilator–free days at day 28				
Median (IQR)			Common odds ratio	---
Secondary outcomes				
Duration of ventilation in survivors, days				
Median (IQR)			Median difference	---
Cumulative fluid balance on days 1-7 after randomization, liters				
Median (IQR)			Median difference	---
Cumulative fluid balance on days 1-7 after start of LUS examination, liters				
Median (IQR)			Median difference	---
Mean serum lactate on days 1-7 after randomization, mmol/L				
Median (IQR)			Median difference	---
Incidence of reintubation during ICU admission – no. (%)			Absolute difference	---
Chest drain placement during ICU admission – no. (%)			Absolute difference	---
Incidence of atrial fibrillation during ICU admission – no. (%)			Absolute difference	---
Incidence of acute kidney injury during ICU admission – no. (%)			Absolute difference	---
Incidence of hypernatremia during ICU admission – no. (%)			Absolute difference	---
Use of hemodynamic monitoring during ICU admission – no. (%)			Absolute difference	---
Chest X-ray performed during ICU admission – no. (%)			Absolute difference	---
Chest computerized tomography performed during ICU admission – no. (%)			Absolute difference	
EQ-5D-5L VAS at day 28			Median difference	---
Length of stay				
Intensive care unit				
Median (IQR)			Median difference	---
Hospital				
Median (IQR)			Median difference	---
Mortality				
Intensive care unit – no. (%)			Absolute difference	---
Hospital – no. (%)			Absolute difference	---
28–day – no. (%)			Hazard ratio	---
90–day – no. (%)			Hazard ratio	---

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviation: LUS is lung ultrasound; IQR is interquartile range; ICU is intensive care unit.

MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN (*Trials* 2023;24:226-236)	UPDATE IN THE SAP* (Closed in November 26, 2025
Definition of AKI	KDIGO ≥ 2	Any KDIGO stage due to data limitations
Subgroup analysis of respiratory failure	Acute respiratory distress syndrome as defined by Berlin criteria	Acute hypoxemic respiratory failure

PROPOSED INSERTS

eTable 1 – Additional Baseline Characteristics

	LUS-guided (*n* =)	Usual Care (*n* =)
Detailed reason of ICU admission – no. (%)		
Planned surgery		
Elective cardiothoracic surgery		
Elective other surgery		
Emergency surgery		
Acute cardiothoracic surgery		
Acute other surgery		
Medical		
Out-of-hospital cardiac arrest		
In-hospital cardiac arrest		
Heart failure		
Sepsis		
Trauma		
Neurological		
Intoxication		
Other		
Reason of intubation – no. (%)		
Respiratory		
Pneumonia		
Pulmonary edema		
Pulmonary embolism		
Aspiration		
Thoracic trauma		
Pulmonary hemorrhage		
Inhalation trauma		
Other		
Non-respiratory		
Sepsis		
Cardiothoracic surgery		
Other surgery		
Trauma		
Intoxication		
Neurological		
Heart failure		
Cardiac arrest		
Other		
Co-existing disorders – no. (%)		
Atrial fibrillation		
Paroxysmal		
Permanent		
Chronic kidney disease		
Stage 2		

Stage 3a	
Stage 3b	
Stage 4	
Stage 5	
Stage unknown	
Heart failure	
NYHA I	
NYHA II	
NYHA III	
NYHA IV	
NYHA unknown	
Chronic obstructive pulmonary disease	
GOLD I	
GOLD II	
GOLD III	
GOLD IV	
GOLD unknown	

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviations: LUS is lung ultrasound; ICU is intensive care unit; NYHA is New York Heart Association classification; GOLD is Global Initiative for Chronic Obstructive Lung Disease.

eTable 2 – Additional Characteristics on the First Day of Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)
Died – no. (%)		
Intervention performed – no. (%)		
Lung ultrasound performed		
Reasons for not performing ultrasound		
Hemodynamically unstable		
Patient refusal		
Patient no present/available		
Lack of time		
Other		
Clinical data		
SOFA		
Central nervous system		
Cardiovascular		
Respiratory		
Coagulation		
Liver		
Renal		
Glasgow coma scale – no. (%)		
15		
13-14		
10-12		
6-9		
< 6		
Mean arterial pressure, mmHg		
Heart rate, beats per minute		
New episode of atrial fibrillation* – no. (%)		
Use of vasopressor – no. (%)		
Noradrenaline		
Dose in 24 hours, mg		
Dopamine		
Dose in 24 hours, mg		

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviations: LUS is lung ultrasound; SOFA is Sequential Organ Failure Assessment.

* > 1 hours and/or therapy started.

eTable 3 – Laboratory Tests and Ventilation Data on the First Day of Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)
Laboratory tests		
Creatinine, µmol/L		
Urea, mmol/L		
Bilirubin, µmol/L		
Platelets, $x10^9$/L		
Lactate, mmol/L		
Sodium, mmol/L		
Chloride, mmol/L		
Arterial blood gas		
pH		
PaO_2, mmHg		
PaO_2 / FiO_2		
$PaCO_2$, mmHg		
Bicarbonate, mmol/L		
Ventilation data		
Mode of ventilation – no. (%)		
Pressure controlled		
Volume controlled		
Pressure support ventilation		
INTELLiVENT-ASV		
SIMV pressure controlled		
SIMV volume controlled		
Pressure regulated volume control		
Other		
Tidal volume, mL		
mL/kg predicted body weight		
Respiratory rate, movements per minute		
Spontaneous, movements per minute		
Minute ventilation, L/min		
PEEP, cmH_2O		
Peak pressure, cmH_2O		
Plateau pressure, cmH_2O		
FiO_2, %		

Data are median (quartile 25^{th} – quartile 75^{th}) or number (percentage).

Abbreviations: LUS is lung ultrasound; SIMV is synchronized intermittent mandatory ventilation; ASV is adaptive support ventilation PEEP is positive end-expiratory pressure.

eTable 4 – Lung Ultrasound on the First Day of Hemodynamic Stabilization

	LUS-guided (*n* =)	Usual Care (*n* =)
Position – no. (%)		
Supine		
Prone		
Significant pleural effusion – no. (%)		
Right-sided		
Left-sided		
Bilateral		
Right 1 – no. (%)		
A-Profile		
B1-Profile		
B2-Profile		
C-Profile		
Could not be evaluated		
Right 2 – no. (%)		
A-Profile		
B1-Profile		
B2-Profile		
C-Profile		
Could not be evaluated		
Right 3 – no. (%)		
A-Profile		
B1-Profile		
B2-Profile		
C-Profile		
Could not be evaluated		
Right 4 – no. (%)		
A-Profile		
B1-Profile		
B2-Profile		
C-Profile		
Could not be evaluated		
Right 5 – no. (%)		
A-Profile		
B1-Profile		
B2-Profile		
C-Profile		
Could not be evaluated		
Right 6 – no. (%)		
A-Profile		
B1-Profile		
B2-Profile		

C-Profile
Could not be evaluated
PLAPS right – no. (%)
Positive
Negative
Could not be evaluated
Left 1 – no. (%)
A-Profile
B1-Profile
B2-Profile
C-Profile
Could not be evaluated
Left 2 – no. (%)
A-Profile
B1-Profile
B2-Profile
C-Profile
Could not be evaluated
Left 3 – no. (%)
A-Profile
B1-Profile
B2-Profile
C-Profile
Could not be evaluated
Left 4 – no. (%)
A-Profile
B1-Profile
B2-Profile
C-Profile
Could not be evaluated
Left 5 – no. (%)
A-Profile
B1-Profile
B2-Profile
C-Profile
Could not be evaluated
Left 6 – no. (%)
A-Profile
B1-Profile
B2-Profile
C-Profile
Could not be evaluated
PLAPS left – no. (%)
Positive
Negative

Could not be evaluated

Data are median (quartile 25th – quartile 75th) or number (percentage).
Abbreviations: LUS is lung ultrasound; PLAPS is posterior and/or lateral alveolar and/or pleural syndrome.

eTable 5 – Fluid Balance Over the Ten Days After Randomization

Day	Daily Fluid Balance, mL/24 hours			Cumulative Fluid Balance, mL/24 hours		
	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviations: LUS is lung ultrasound.

* *p* value from an interaction between randomization group and time (as continuous variable) in a mixed-effect model.

eTable 6 – Fluid Intake, Output and Balance Over the First Ten Days After Randomization

Day	Fluid Intake, mL/24 hours			Fluid Output, mL/24 hours		
	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviations: LUS is lung ultrasound.

* *p* value from an interaction between randomization group and time (as continuous variable) in a mixed-effect model.

eTable 7 – Sequential Organ Failure Assessment Over the First Ten Days After Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
Total SOFA			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Cardiovascular SOFA			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Respiratory SOFA			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Renal SOFA			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			

Data are median (quartile 25th – quartile 75th) or number (percentage).
Abbreviations: LUS is lung ultrasound; SOFA is Sequential Organ Failure Assessment.
* *p* value from an interaction between randomization group and time (as continuous variable) in a mixed-effect model.

eTable 8 – Use and Dose of Vasopressor Over the First Ten Days After Randomization

Day	Use of Vasopressor, %			Vasopressor Dose**, mg		
	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviations: LUS is lung ultrasound.

* *p* value from an interaction between randomization group and time (as continuous variable) in a mixed-effect model.

** In noradrenaline equivalents.

eTable 9 – Laboratory Tests Over the First Ten Days After Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
Lactate, mmol/L			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Creatinine, µmol/L			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Sodium, mmol/L			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Chloride, mmol/L			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
PaO_2 / FiO_2			
Day 1			
Day 2			
Day 3			

eTable 9 – Laboratory Tests Over the First Ten Days After Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			

Data are median (quartile 25th – quartile 75th) or number (percentage).
Abbreviations: LUS is lung ultrasound.
* *p* value from an interaction between randomization group and time (as continuous variable) in a mixed-effect model.

eTable 10 – Ventilation Variables Over the First Ten Days After Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
Tidal volume, mL/kg predicted body weight			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
PEEP, cmH_2O			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Peak pressure, cmH_2O			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Plateau pressure, cmH_2O			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			

eTable 10 – Ventilation Variables Over the First Ten Days After Randomization

	LUS-guided (*n* =)	Usual Care (*n* =)	*p* value*
Day 10			
FiO_2, cmH_2O			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			

Data are median (quartile 25th – quartile 75th) or number (percentage).

Abbreviations: LUS is lung ultrasound; PEEP is positive end-expiratory pressure.

* *p* value from an interaction between randomization group and time (as continuous variable) in a mixed-effect model.

eTable 12 – Additional Outcomes

	LUS-guided (*n* =)	Usual Care (*n* =)
28-day mortality – no. (%)		
Multiorgan failure		
Cardiac failure		
Respiratory failure		
Bleeding		
Malignancy		
Sepsis		
Limitation of care		
Other		
Incidence of acute kidney injury – no. (%)		
Days between randomization and acute kidney injury		
Received renal replacement therapy during ICU admission – no. (%)		
Tracheostomy – no. (%)		
Days between randomization and tracheostomy		
Chest drain placement during ICU admission – no. (%)		
Number of drains inserted		
Chest X-ray performed during ICU admission – no. (%)		
Number of X-rays performed		
Chest CT scan performed during ICU admission – no. (%)		
Number of CT scans performed		
Development of acute respiratory distress syndrome – no. (%)		
Mild		
Moderate		
Severe		
Development of sepsis – no. (%)		

Data are median (quartile 25th – quartile 75th) or number (percentage).
Abbreviations: LUS is lung ultrasound; CT is computed tomography.