Statistical Analysis Plan of the 'Restricted versus Liberal Positive End–expiratory Pressure in Patients Without ARDS trial' (RELAx)

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INTRODUCTION

The 'REstricted versus Liberal positive end–expiratory pressure in patients without ARDS trial' (RELAx) compares two positive end–expiratory pressure (PEEP) strategies in intensive care unit (ICU) patients without acute respiratory distress syndrome (ARDS) at onset of invasive ventilation [1]. The primary objective of this study is to determine whether a ventilation strategy with the lowest possible PEEP between 0 and 5 cmH_2O ('restricted PEEP') is noninferior to a ventilation strategy with prophylactic high PEEP of 8 cmH_2O ('liberal PEEP') with regard to the number of ventilator–free days and alive at day 28. Enrollment of patients in RELAx is ongoing and completion of inclusion is expected to occur in the first trimester of 2020.

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 RELAx.

METHODS

Design

The protocol, with a detailed description of the study population, the two interventions and follow–up plan of RELAx was published before [1]. RELAx is registered in clinicaltrials.gov (study identifier NCT03167580) and is approved by the Institutional Review Board of the Amsterdam University Medical Centers, location Academic Medical Center, in Amsterdam, The Netherlands (2017_074#B2017434). RELAx is an investigator–initiated national multicenter parallel pragmatic two–arm randomized clinical noninferiority trial, comparing a ventilation strategy with the lowest possible PEEP between 0 and 5 cmH_2O ('restricted PEEP') with a ventilation strategy with prophylactic high PEEP of 8 cmH_2O ('liberal PEEP') in ICU patients without ARDS at start of invasive ventilation. Currently, the study enrolls patients in the ICUs of eight hospitals in The Netherlands.

Randomization and blinding

Eligible patients are randomly allocated in a 1:1 ratio to the 'restricted PEEP' or the 'liberal PEEP' strategy. Randomization is performed using a dedicated, password protected, SSL–encrypted website with ALEA® software (TenALEA consortium, Amsterdam, The Netherlands) using random block sizes (maximum size of 8). 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 during the first 28 days. Patients who die within 28 days or are still invasively ventilated after 28 days will be assigned 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;
- Incidence of new ARDS;
- Incidence of suspected ventilator–associated pneumonia (VAP);
- Incidence of confirmed VAP;
- Incidence of severe atelectasis, if a chest radiograph or other kind of imaging suitable for diagnosing atelectasis is obtained;
- Incidence of severe hypoxemia;
- Incidence of pneumothorax, if a chest radiograph or other kind of imaging suitable for diagnosing pneumothorax is obtained;
- Need for rescue strategies for severe hypoxemia or severe atelectasis;
- Days with hemodynamic support;
- Days with sedation;
- ICU length of stay;
- Hospital length of stay;
- ICU mortality;
- Hospital mortality;
- 28–day mortality; and
- 90–day mortality.

Originally, duration of ventilation in survivors and 28–day mortality was not included as secondary outcomes. However, following a recent discussion in the

field on the use of ventilator–free days as an outcome [2], this is now added. Data regarding extra–pulmonary complications (sepsis, extra–pulmonary infection, re–operation and cardiac arrest) are also collected but not considered outcomes of the study.

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 980 patients are enrolled. This number of patients was expected to be sufficient to show noninferiority of the ‘restricted PEEP’ versus the ‘liberal PEEP’ strategy with a noninferiority margin of 10%, assuming no difference in the number of ventilator–free days in both groups, a mean and common standard deviation in ventilator–free days of 16 and 10,

respectively [3,4], a one–sided alpha level of 5%, 80% of power, similar allocation of subjects to each group and corrected for 10% of dropouts. This power calculation was based on the expected duration of invasive ventilation of 5 days, with an associated coefficient of variation of 0.7 days and with a 28–day mortality around 30%, as found in other studies in the same population [3,4].

The choice of a noninferiority margin of 10% was motivated by what could be considered acceptable from a clinical point of view. This margin means that a difference of less than 12 hours in duration of ventilation or 1.6 ventilator–free days with the 'restricted PEEP' strategy will be considered noninferior to the 'liberal PEEP' strategy.

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. The primary outcome will be assessed using a one–sided noninferiority hypothesis test with a significance level of 0.05 and presented with a one–sided 95% confidence interval. If noninferiority is confirmed, superiority of 'restricted PEEP' will be tested considering a 95% confidence interval for the primary outcome. Since the proposed approach will use a hierarchical closed–testing procedure examining a single confidence interval, no adjustment of the overall type I error will be done [5,6].

All analyses of secondary outcomes 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 ventilation strategies

Daily ventilation variables and parameters will be reported according to the **Table 4.** Absolute differences between the groups with the respective 95% confidence interval will be calculated as mean difference from a mixed–effect linear model considering the centres as random effect to account for within–center clustering. PEEP, inspired fraction of oxygen (FiO_2) and pulse oximetry (SpO_2) are recorded every six hours (02:00h, 08:00h, 14:00h and 20:00h) and the daily value per patient will be summarized as the mean for PEEP and FiO_2 and time–weighted mean for SpO_2 and SpO_2 / FiO_2, calculated according to equation 1 and 2 below. In addition, the highest and lowest daily entrees for PEEP, FiO_2, SpO_2 and SpO_2 / FiO_2 will be reported as outlined in **Table 2**.

$$AUC = \frac{1}{2}\sum_{i=0}^{n-1}(t_{i+1} - t_i)(y_i + y_{i+1}) \ (Eq.\ 1)$$

where y_1 and y_2 are measurements at time t_1 and t_2

$$Tw = \frac{AUC}{n_{observations}} \ (Eq.\ 2)$$

where AUC is the area under the curve calculated according Eq. 1 and $n_{observations}$ are the number of observations available in the period in hours

The difference in PEEP, SpO_2, FiO_2, driving pressure, SpO_2/FiO_2, PaO_2, $PaCO_2$, $etCO_2$, heart rate and mean arterial pressure among the groups from the pre–randomization until day five will be presented 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 day 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. To further explore the gradient between the groups, PEEP, FiO_2 and SpO_2 will be presented in cumulative distribution plots for the first three days of ventilation (**Table 2**).

Separation between groups

To assess the separation between the study arms, the total number of observations and the proportion of observations with PEEP, SpO_2 and FiO_2 outside proposed targets in the first five days of ventilation or until extubation, if occurred earlier, will be calculated from the records taken every six hours daily

and reported as in **Table 5**. The results will be presented as medians and median difference calculated from a median regression with 95% confidence intervals.

Other daily characteristics

Daily variables, including sedation, transfusion, fluid therapy and use of vasoactive drugs will be reported according to the **Table 6**. The percentage of patients under light sedation (defined as a RASS –2 to +1) and deep sedation (defined as a RASS –5 to –3) will be calculated and reported. 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 centres as random effect to account for within–center clustering in continuous variables and as risk differences derived from a generalized linear model considering a binomial distribution with an identity-link and with centres as random effect to account for within–center clustering for categorical variables.

Primary outcome

The effect of 'restricted PEEP' compared to 'liberal PEEP' on the ventilator–free days at day 28 will be presented as a mean ratio (as described in the Eq. 3 below), tested for noninferiority considering a margin of 10%, as explicitly stated in the protocol and sample size calculation, and presented as a one–sided 95% confidence interval. Thus, noninferiority will be established if lower boundary of the one–sided 95% confidence interval was higher than 0.90 (10% decrease in ventilator–free days at day 28). To increase transparency, the data will be presented by group as means ± standard deviations and also medians (quartiles 25% – quartiles 75%). Since ventilator–free days is a highly skewed variable with a peak in 0 due to 28–day mortality (expected to be around 30% according to previous studies in the same population [3,4]), the mean ratio will be estimated

using a generalized additive model for location scale and shape (GAMLSS) considering a zero–inflated beta distribution and using the delta method to estimate the confidence interval. A one–sided *p* value for noninferiority will be calculated and provided as described in the Eq. 4. Results will be presented in a table of outcomes (**Table 7**) and also in a forest plot as shown in **Figure 2** considering simulated data.

$$Mean\ Ratio = \frac{Mean_{VFD}\ in\ Low\ PEEP}{Mean_{VFD}\ in\ Liberal\ PEEP} > 0.90\ (Eq.\ 2)$$

$$p\ value = 1 - pnorm\ (\frac{Estimate - 0.90}{SE})\ (Eq.\ 3)$$

where pnorm is the cumulative distribution function of normal distribution, estimate is the mean ratio estimated by the model, 0.90 is the noninferiority margin, and SE is the standard error

As an additional and sensitivity analysis for the primary outcome, ventilator–free days at day 28 in both groups will be compared using a median difference from a median regression and presented also as a one–sided 95% confidence interval with the margin of noninferiority set at 10% of the median of ventilator–free days at day 28 in the 'liberal PEEP' arm. For this sensitivity analysis no *p* value will be calculated.

A final additional analysis will be done considering a generalized pairwise comparison. This analysis will be calculated in such a manner that death constitutes a worse outcome than fewer days off the ventilator. Each patient will be compared to every other patient in the study and assigned a score (0, +1, -1) for each pairwise comparison based on whom fared better. For each patient, scores for all pairwise comparisons will be summed, resulting in a cumulative score for each patient. These cumulative scores will be ranked and compared

between treatment groups via the Wilcoxon rank-sum technique. Effect size will be reported as the probability of superior outcome, also known as the probabilistic index, which describes the estimated probability that an individual randomly selected from one treatment group will have a higher score (more favorable outcome) than an individual randomly selected from the other group.

Secondary outcomes

As stated above, all analyses of the secondary outcomes will be two–sided and assessing superiority (**Table 7**). The number and percentages of ARDS, suspected and confirmed VAP, severe atelectasis, severe hypoxemia, pneumothorax, need for rescue strategies, and ICU– and hospital mortality be reported. The effect of the intervention on these binomial outcomes will be assessed with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing. The duration of ventilation in survivors, and the ICU– and hospital length of stay will be presented as mean ± standard deviation and median (quartile 25% – quartile 75%) and compared using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates. Also, 28– and 90–day mortality will be presented as number and percentages and compared using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality assumption is not sustained. The days with hemodynamic support and sedation will be presented as mean ±

standard deviation and median (quartile 25% – quartile 75%) and compared as the mean difference among the groups from an independent *t*–test.

All comparisons among the secondary outcomes will also be presented as absolute differences with continuous outcome being presented as mean difference from a mixed–effect linear model considering the centres as random effect to account for within–center clustering in continuous outcomes and as risk differences derived from a generalized linear model considering a binomial distribution with an identity–link and with centres as random effect to account for within–center clustering for binary outcomes. In addition, a Holm–Bonferroni correction to control the family–wide error rate to the *p* values for all 16 secondary outcomes will be done and presented in a Table.

Per–protocol analysis

The per–protocol analysis only considers those patients who completed PEEP titrations according to the originally allocated treatment study protocol. Patients assigned to the 'restricted PEEP' strategy will be excluded for the per–protocol analysis if receiving PEEP > 5 cm H_2O for the first 2 days while ventilation was not executed according to the boundaries that were imposed by the study protocol, namely: if in at least two of the four measurements per day PEEP > 5 cmH_2O and $FiO_2 \leq 0.6$ or SpO2 > 92% the patient will be excluded. Patients assigned to the 'liberal PEEP' strategy will be excluded for the per–protocol analysis if receiving PEEP < 8 cm H_2O for the first 2 days while ventilation was not executed according to the boundaries that were imposed by the study protocol, namely: if in at least two of the four measurements per day PEEP < 8 cmH_2O and the patient did not have any documented hemodynamic instability the patient will be excluded.

Additional analysis

As additional analyses, the duration of ventilation in survivors, and the time until ICU and hospital discharge will be assessed in a competing risk model with death before extubation, ICU discharge or hospital discharge, respectively, treat as competing risk. The results will be described with the use of cumulative incidence function and reported as subdistribution hazard ratio with 95% confidence interval estimated from a Fine–Gray model.

As a further sensitivity analysis, the effect of the intervention on primary and secondary outcomes will be re–estimated using mixed–effect or (shared–frailty) Cox models with patients nested in centres and centres treated as random effect and incorporating adjustment for age, gender, prognostic score as well as for any observed baseline differences. These models will incorporate the underling 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 GAMLSS considering a zero–inflated beta distribution irrespective of whether there is evidence of a treatment effect. Results will be summarized by subgroup and presented as mean ratios 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 number 0.90 (margin of noninferiority). The following subgroups will be assessed:

- Non–surgical vs. surgical admission;
- Cardiac arrest vs. non–cardiac arrest;
- Respiratory failure vs. non–respiratory failure;
- Body mass index > 30 kg/m^2 vs. body mass index ≤ 30 kg/m^2;
- Admission $PaO_2/FiO_2 \leq 200$ vs. Admission $PaO_2 / FiO_2 > 200$;
- Lung Injury Prediction Score (LIPS) ≥ 4 vs. LIPS < 4; and
- SAPS II ≥ 50 vs. SAPS II < 50.

SUMMARY

RELAx is an investigator–initiated national multicenter parallel pragmatic two–arm randomized clinical noninferiority trial. This trial will compare a ventilation strategy with ‘restricted PEEP’ with a ventilation strategy with ‘liberal PEEP’ in 980 adults without ARDS 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

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Table 1 – Definitions of secondary outcomes

Outcomes	Definition
Ventilator–free days at day 28	Start time: day of randomization (the same as the day of intubation due to the strict time for inclusion) 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. Only patients surviving the first 28 days will be considered.
Incidence of new ARDS	According to the Berlin definition[a] Only ARDS developing after the first 48 hours of randomization will be considered and the degree of severity will be reported
Incidence of early or late suspected VAP	New or progressive radiographic infiltrate plus at least two of the following: • Temperature > 38.5ºC; and/or • Leukocytosis (> 12,000 cells/mm^3) or leucopenia (< 4,000 cells/$mm^{3)}$; and/or • Purulent secretions. Patients were intubated and mechanically ventilated for at least 48 hours.
Incidence of early or late confirmed VAP	New or progressive radiographic infiltrate, with microbiological confirmation and plus at least two of the following: • Temperature > 38.5ºC; and/or • Leukocytosis (> 12,000 cells/mm^3) or leucopenia (< 4,000 cells/$mm^{3)}$; and/or • Purulent secretions. Patients were mechanically ventilated for at least 48 hours.
Incidence of early or late severe atelectasis	At least complete lobar atelectasis of a lung on chest radiograph or other kind of imaging suitable for diagnosis severe atelectasis
Incidence of early or late severe hypoxemia	SpO_2 < 88% or PaO_2 < 7.3 kPa (< 55 mmHg) and needing a rise of the oxygen fraction to more 0.6 and/or a rise of the PEEP level to more than 5 cmH_2O (in restriced PEEP arm) or more than 8 cmH_2O (in liberal PEEP arm)
Incidence of early or late 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.
Need for early or late rescue strategies for severe hypoxemia or severe atelectasis	Need of one of the following: • Recruitment maneuvers; and/or • Prone positioning; and/or • Bronchoscopy for opening atelectasis The maneuvers will be reported as a collapsed composite of need for rescue and also individually

Days with hemodynamic support	Number of ICU days with any use of continious infusion vasopressors/inotropes for more than 1 hour on a day.
Days with sedation	Number of ICU days with any use of continious infusion sedatives for more than 1 hour on a day.
ICU length of stay	Number of days from ICU admission till ICU discharge
Hospital length of stay	Number of days from hospital admission 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

ARDS: acute respiratory distress syndrome; VAP: ventilator–associated pneumonia; ICU intensive care unit

[A] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.

Table 2 – List of proposed tables and figures

	Description
Main paper	
Table 1	Baseline characteristics of the included patients
Table 2	Primary and secondary outcomes
Figure 1	Participant flow diagram
Figure 2	Forest plot for the non–inferiority analysis of the primary outcome *A forest plot showing the mean ratio with the one–sided 95% confidence interval for the comparison of ventilator–free days at day 28 among the restricted PEEP and liberal PEEP group with the non–inferiority margin set at 0.90*
Figure 3	Kaplan–Meier estimates for patients in the Restricted PEEP and Liberal PEEP groups *A four panels figure showing: A) Kaplan–Meier curve for the time until freedom of invasive ventilation in both groups; B) Kaplan–Meier curve for the 90–day survival in both groups; C) Kaplan–Meier curve for the time until intensive care unit discharge in both groups; and D) Kaplan–Meier curve for the time until hospital discharge in both groups For each panel an unadjusted hazard ratio and 95% confidence interval calculated from a Cox proportional hazard model will be presented*
Online Supplement	
Table S1	Daily ventilatory variables, vital signs and arterial blood gases in the first three days after randomization
Table S2	Separation of the treatments
Table S3	Daily sedation, fluids, transfusion and vasoactive drugs
Table S4	Multiplicity adjustment for secondary outcome analyses *A table showing the observed p values for all the secondary outcomes and ordered from the lower until the higher and the corrected p values using a Holm–Bonferroni correction*
Table S5	Primary and secondary outcomes after adjustment for clustering effect of centres and baseline variables *Re–estimation of the effect of the intervention on primary and secondary outcomes using mixed–effect or (shared–frailty) Cox models with patients nested in centres and centres treated as random effect and incorporating adjustment for age, gender, SAPS II score as well as for any observed baseline differences. These models will incorporate the underling distribution of each outcome as described in the secondary outcomes section.*
Figure S1	Management of patients according to the allocated arm
Figure S2A	Mean PEEP by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and PEEP on the vertical axis with mean daily PEEP shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily PEEP will be calculated from recordings of PEEP taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S2B	Highest PEEP by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and PEEP on the vertical axis with highest daily PEEP shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest daily PEEP will be recorded from recordings of PEEP taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S2C	Lowest PEEP by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and PEEP on the vertical axis with lowest daily PEEP shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest daily PEEP will be recorded from recordings of PEEP taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S3A	Mean FiO_2 by treatment group over the first five days of ventilation

	Line graph with days 0 to 5 on the horizontal axis and FiO_2 on the vertical axis with mean daily FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily FiO_2 will be calculated from recordings of FiO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.
Figure S3B	Highest FiO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and FiO_2 on the vertical axis with highest daily FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest daily FiO_2 will be recorded from recordings of FiO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S3C	Lowest FiO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and FiO_2 on the vertical axis with lowest daily FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest daily FiO_2 will be recorded from recordings of FiO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S4A	Time–weighted mean SpO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and SpO_2 on the vertical axis with time–weighted mean daily SpO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The time–weighted mean daily SpO_2 will be calculated from recordings of SpO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S4B	Highest SpO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and SpO_2 on the vertical axis with highest daily SpO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest daily SpO_2 will be recorded from recordings of SpO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S4C	Lowest SpO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and SpO_2 on the vertical axis with lowest daily SpO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest daily SpO_2 will be recorded from recordings of SpO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S5A	Time–weighted mean SpO_2 / FiO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and SpO_2 / FiO_2 on the vertical axis with time–weighted mean daily SpO_2 / FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The time–weighted mean daily SpO_2/ FiO_2 will be calculated from recordings of SpO_2 and FiO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S5B	Highest SpO_2 / FiO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and SpO_2 / FiO_2 on the vertical axis with highest daily SpO_2 / FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Highest daily SpO_2 / FiO_2 will be recorded from recordings of SpO_2 and FiO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S5C	Lowest SpO_2 / FiO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and SpO_2 / FiO_2 on the vertical axis with lowest daily SpO_2 / FiO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. Lowest daily SpO_2 / FiO_2 will be recorded from recordings of SpO_2 and FiO_2 taken six hourly while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S6	Mean driving pressure by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and driving pressure on the vertical axis with mean daily driving pressure shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily driving pressure will be calculated from the record of PEEP taken closest to the daily measurement*

	of plateau pressure while the patient is invasively ventilated in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.
Figure S7	Mean PaO_2 by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and PaO_2 on the vertical axis with mean daily PaO_2 shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily PaO_2 will be calculated from the daily collected PaO_2 in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S8	Mean $PaCO_2$ by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and $PaCO_2$ on the vertical axis with mean daily $PaCO_2$ shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily $PaCO_2$ will be calculated from the daily collected $PaCO_2$ in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S9	Mean $etCO_2$ by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and $etCO_2$ on the vertical axis with mean daily $etCO_2$ shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily $etCO_2$ will be calculated from the daily collected $etCO_2$ in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S10	Mean heart rate by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and heart rate on the vertical axis with mean daily heart rate shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily heart rate will be calculated from the daily collected heart rate in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S11	Mean mean arterial pressure by treatment group over the first five days of ventilation *Line graph with days 0 to 5 on the horizontal axis and mean arterial pressure on the vertical axis with mean daily mean arterial pressure shown by treatment group. The number of observations by group on each day will be indicated on the horizontal axis. The mean daily mean arterial pressure will be calculated from the daily collected mean arterial pressure in the ICU up until day 5. Data points will be reported with corresponding 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
Figure S12A	Cumulative distribution of mean PEEP after randomization *Cumulative distribution plot showing the mean PEEP after randomization by treatment group. The mean PEEP will be calculated from recordings of PEEP taken six hourly*
Figure S12B	Cumulative distribution of mean PEEP at day 1 of ventilation *Cumulative distribution plot showing the mean PEEP at day 1 by treatment group. The mean PEEP will be calculated from recordings of PEEP taken six hourly*
Figure S12C	Cumulative distribution of mean PEEP at day 2 of ventilation *Cumulative distribution plot showing the mean PEEP at day 2 by treatment group. The mean PEEP will be calculated from recordings of PEEP taken six hourly*
Figure S12D	Cumulative distribution of mean PEEP at day 3 of ventilation *Cumulative distribution plot showing the mean PEEP at day 3 by treatment group. The mean PEEP will be calculated from recordings of PEEP taken six hourly*
Figure S13A	Cumulative distribution of mean FiO_2 after randomization *Cumulative distribution plot showing the mean FiO_2 after randomization by treatment group. The mean FiO_2 will be calculated from recordings of FiO_2 taken six hourly*
Figure S13B	Cumulative distribution of mean FiO_2 at day 1 of ventilation *Cumulative distribution plot showing the mean FiO_2 at day 1 by treatment group. The mean FiO_2 will be calculated from recordings of FiO_2 taken six hourly*
Figure S13C	Cumulative distribution of mean FiO_2 at day 2 of ventilation *Cumulative distribution plot showing the mean FiO_2 at day 2 by treatment group. The mean FiO_2 will be calculated from recordings of FiO_2 taken six hourly*
Figure S13D	Cumulative distribution of mean FiO_2 at day 3 of ventilation *Cumulative distribution plot showing the mean FiO_2 at day 3 by treatment group. The mean FiO_2 will be calculated from recordings of FiO_2 taken six hourly*
Figure S14A	Cumulative distribution of time–weighted mean SpO_2 after randomization *Cumulative distribution plot showing the time–weighted mean SpO_2 after randomization by treatment group. The time–weighted mean SpO_2 will be calculated from recordings of SpO_2 taken six hourly*

Figure S14B	Cumulative distribution of time–weighted mean SpO_2 at day 1 of ventilation *Cumulative distribution plot showing the time–weighted mean SpO_2 at day 1 by treatment group. The time–weighted mean SpO_2 will be calculated from recordings of SpO_2 taken six hourly*
Figure S14C	Cumulative distribution of time–weighted mean SpO_2 at day 2 of ventilation *Cumulative distribution plot showing the time–weighted mean SpO_2 at day 2 by treatment group. The time–weighted mean SpO_2 will be calculated from recordings of SpO_2 taken six hourly*
Figure S14D	Cumulative distribution of time–weighted mean SpO_2 at day 3 of ventilation *Cumulative distribution plot showing the time–weighted mean SpO_2 at day 3 by treatment group. The time–weighted mean SpO_2 will be calculated from recordings of SpO_2 taken six hourly*
Figure S15	Modes of ventilation by treatment group *Clustered stacked bar chart with day 0 to day 5 on the horizontal axis, percentage of patients on the vertical axis, clustered according to the allocated arm and stacked according to the mode of ventilation. Seven modes will be considered: volume–controlled ventilation, pressure–controlled ventilation, pressure support ventilation, adaptive support ventilation, synchronized intermittent mandatory volume–controlled ventilation, synchronized intermittent mandatory pressure–controlled ventilation and other.*
Figure S16	Sensitivity analysis for the primary outcome *A forest plot showing the median difference with the one–sided 95% confidence interval for the comparison of ventilator–free days at day 28 among the restricted PEEP and liberal PEEP group with the non–inferiority margin set at 10% of the median in the liberal PEEP arm*
Figure S17	Kaplan–Meier estimates for patients in the Restricted PEEP and Liberal PEEP groups *A Kaplan–Meier curve for the 28–day survival in both groups. An unadjusted hazard ratio and 95% confidence interval calculated from a Cox proportional hazard model will be presented*
Figure S18	Time–to–event analysis for duration of ventilation *A two panel figure showing: A) Kaplan–Meier curve for the time until freedom of invasive ventilation in survivors in both groups and with an unadjusted hazard ratio and 95% confidence interval calculated from a Cox proportional hazard model; B) Cumulative Incidence Function for the time until freedom of invasive ventilation in all patients in both groups with death before extubation treated as competing risk and with an unadjusted subsdistribution hazard ratio and 95% confidence interval calculated from a Fine–Gray model*
Figure S19	Time–to–event analysis for ICU discharge *A two panel figure showing: A) Kaplan–Meier curve for the time until ICU discharge in both groups with and with an unadjusted hazard ratio and 95% confidence interval calculated from a Cox proportional hazard model; B) Cumulative Incidence Function for the time until ICU discharge in both groups with death before ICU discharge treated as competing risk and with an unadjusted subsdistribution hazard ratio and 95% confidence interval calculated from a Fine–Gray model*
Figure S20	Time–to–event analysis for hospital discharge *A two panel figure showing: A) Kaplan–Meier curve for the time until hospital discharge in both groups with and with an unadjusted hazard ratio and 95% confidence interval calculated from a Cox proportional hazard model; B) Cumulative Incidence Function for the time until hospital discharge in both groups with death before hospital discharge treated as competing risk and with an unadjusted subsdistribution hazard ratio and 95% confidence interval calculated from a Fine–Gray model*
Figure S21	Subgroup analysis *A forest plot showing the mean ratio and two–sided 95% confidence intervals with p value for interaction calculated via a test for treatment–by–subgroup interaction in the GAMLSS considering a zero–inflated beta distribution. A solid line of reference in the number 1 and a dashed line of reference in the number 0.90 (margin of non–inferiority) will be shown.*

Table 3 – Baseline characteristics of the patients

	Restricted PEEP (*n* =)	Liberal PEEP (*n* =)
Age, years		
Female sex		
BMI, kg/m^2		
PBW, kg		
SAPS II score		
LIPS score		
Patients at risk for ARDS		
SOFA score		
Septic shock		
Tobacco use		
Never		
Current		
Previous		
Former		
Unknown		
Reason of ICU admission		
Planned surgery		
Emergency surgery		
Medical		
Reason of intubation		
Cardiac arrest		
Planned postoperative ventilation		
Depressed level of consciousness		
Respiratory failure		
Hours ventilated before randomization		
Ventilatory variables		
Mode of ventilation		
Pressure–controlled		
Volume–controlled		
Pressure support		
Other		
Tidal volume, mL/kg PBW		
Plateau pressure, cmH_2O		
Respiratory rate, bpm		
PEEP, cmH_2O		
Driving pressure, cmH_2O		
FiO_2		
PaO_2 / FiO_2, mmHg		
$PaCO_2$, mmHg		
Arterial pH		
SpO_2, %		
SpO_2 / FiO_2		
$etCO_2$, mmHg		
Heart rate, bpm		
Mean arterial pressure, mmHg		

BMI: body mass index; SAPS: Simplified Acute Physiology Score; LIPS: Lung Injury Prediction Score; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; PBW: predicted body weight; bpm: breaths per minute; PEEP: positive end-expiratory pressure

Table 4 – Daily ventilatory variables, vital signs and arterial blood gases in the first three days after randomization

	After randomization				Day 01			
	Restricted PEEP	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**	**Restricted PEEP**	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**
Number of patients								
PEEP, cmH_2O								
Tidal volume, mL/kg PBW								
Plateau pressure, cmH_2O								
Driving pressure, cmH_2O								
Respiratory rate, bpm								
FiO_2								
PaO_2 / FiO_2, mmHg								
$PaCO_2$, mmHg								
Arterial pH								
SpO_2, %								
SpO_2 / FiO_2								
$etCO_2$, mmHg								
Heart rate, bpm								
MAP, mmHg								

PBW: predicted body weight; bpm: breaths per minute; PEEP: positive end-expiratory pressure; MAP: mean arterial pressure

Table 4 – Daily ventilatory variables, vital signs and arterial blood gases in the first three days after randomization

	Day 02				Day 03			
	Restricted PEEP	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**	**Restricted PEEP**	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**
Number of patients								
PEEP, cmH_2O								
Tidal volume, mL/kg PBW								
Plateau pressure, cmH_2O								
Driving pressure, cmH_2O								
Respiratory rate, bpm								
FiO_2								
PaO_2 / FiO_2, mmHg								
$PaCO_2$, mmHg								
Arterial pH								
SpO_2, %								
SpO_2 / FiO_2								
$etCO_2$, mmHg								
Heart rate, bpm								
MAP, mmHg								

PBW: predicted body weight; bpm: breaths per minute; PEEP: positive end-expiratory pressure; MAP: mean arterial pressure

Table 5 – Separation of the treatments*

	Restricted PEEP (*n* =)	Liberal PEEP (*n* =)	Median Difference (95% CI)
Measurements PEEP ≤ 5 cmH_2O			
Median (IQR) proportion of measurements per patient PEEP ≤ 5 cmH_2O			
Median (IQR) number of observations per patient PEEP ≤ 5 cmH_2O			
Measurements PEEP < 5 cmH_2O			
Median (IQR) proportion of measurements per patient PEEP < 5 cmH_2O			
Median (IQR) number of observations per patient PEEP < 5 cmH_2O			
Measurements PEEP 0 cmH_2O			
Median (IQR) proportion of measurements per patient PEEP 0 cmH_2O			
Median (IQR) number of observations per patient PEEP 0 cmH_2O			
Measurements PEEP 8 cmH_2O			
Median (IQR) proportion of measurements per patient PEEP 8 cmH_2O			
Median (IQR) number of observations per patient PEEP 8 cmH_2O			
Measurements PEEP > 8 cmH_2O			
Median (IQR) proportion of measurements per patient PEEP > 8 cmH_2O			
Median (IQR) number of observations per patient PEEP > 8 cmH_2O			
Measurements FiO_2 > 0.6			
Median (IQR) proportion of measurements per patient FiO_2 > 0.6			
Median (IQR) number of observations per patient FiO_2 > 0.6			
Measurements FiO_2 1.0			
Median (IQR) proportion of measurements per patient FiO_2 1.0			
Median (IQR) number of observations per patient FiO_2 1.0			
Measurements FiO_2 0.21			
Median (IQR) proportion of measurements per patient FiO_2 0.21			
Median (IQR) number of observations per patient FiO_2 0.21			
Measurements SpO_2 < 92%			
Median (IQR) proportion of measurements per patient SpO_2 < 92%			
Median (IQR) number of observations per patient SpO_2 < 92%			
Measurements SpO_2 < 88%			
Median (IQR) proportion of measurements per patient SpO_2 < 88%			
Median (IQR) number of observations per patient SpO_2 < 88%			
Measurements SpO_2 > 96%			
Median (IQR) proportion of measurements per patient SpO_2 > 96%			
Median (IQR) number of observations per patient SpO_2 > 96%			

* PEEP, FiO_2 and SpO_2 will be obtained from values recorded every six hours until day 5 post randomization or until extubation

Table 6 – Daily sedation, fluids, transfusion and vasoactive drugs

	After randomization				Day 01			
	Restricted PEEP	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**	**Restricted PEEP**	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**
Number of patients								
Sedation								
Lowest RASS								
Light sedation								
Deep sedation								
Sedative infusion								
Hours under sedation								
Fluids								
Volume of crystalloids, mL								
Volume of colloids, mL								
Cumulative fluid balance, mL								
Transfusion								
Packed red blood cells								
Units								
Fresh frozen plasma								
Units								
Platelets								
Units								
Vasoactive drugs								
Vasoactive drugs infusion								
Hours under vasoactive								
SOFA score								

RSAS: Richmond Agitation Sedation Scale; SOFA: Sequential Organ Failure Assessment

Table 6 – Daily sedation, fluids, transfusion and vasoactive drugs

	Day 02				Day 03			
	Restricted PEEP	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**	**Restricted PEEP**	**Liberal PEEP**	**Absolute Difference (95% CI)**	***p* value**
Number of patients								
Sedation								
Lowest RASS								
Light sedation								
Deep sedation								
Sedative infusion								
Hours under sedation								
Fluids								
Volume of crystalloids, mL								
Volume of colloids, mL								
Cumulative fluid balance, mL								
Transfusion								
Packed red blood cells								
Units								
Fresh frozen plasma								
Units								
Platelets								
Units								
Vasoactive drugs								
Vasoactive drugs infusion								
Hours under vasoactive								
SOFA score								

RSAS: Richmond Agitation Sedation Scale; SOFA: Sequential Organ Failure Assessment

Table 7 – Primary and secondary outcomes

	Restricted PEEP (*n* =)	Liberal PEEP (*n* =)	Absolute Difference (95% CI)	Effect Estimate (95% CI)	*p* value	
					Non–inferiority	Superiority
Primary outcome Ventilator–free days at day 28 Median (IQR)			MD*	MR*	**	
Secondary outcomes						
Duration of ventilation in survivors, days Median (IQR)			MD	HR	---	
Acute respiratory distress syndrome			RD	RR	---	
Suspected ventilator–associated pneumonia			RD	RR		
Confirmed ventilator–associated pneumonia			RD	RR	---	
Severe atelectasis			RD	RR	---	
Severe hypoxemia			RD	RR	---	
Pneumothorax			RD	RR	---	
Need for rescue strategies			RD	RR	---	
Recruitment maneuvers			RD	RR	---	
Prone positioning			RD	RR	---	
Bronchoscopy for atelectasis			RD	RR	---	
Days with hemodynamic support Median (IQR)			MD	MD	---	
Days with sedation Median (IQR)			MD	MD	---	
Length of stay					---	
ICU Median (IQR)			MD	HR	---	
Hospital Median (IQR)			MD	HR	---	
Mortality					---	
ICU			RD	RR	---	
Hospital			RD	RR	---	
28–day			RD	HR	---	
90–day			RD	HR	---	

MD: mean difference; MR: mean ratio; ICU: intensive care unit; RD: risk difference; RR: risk ratio; HR: hazard ratio

* presented as one–sided 95% confidence interval; ** *p* value for non–inferiority with a margin of 10%

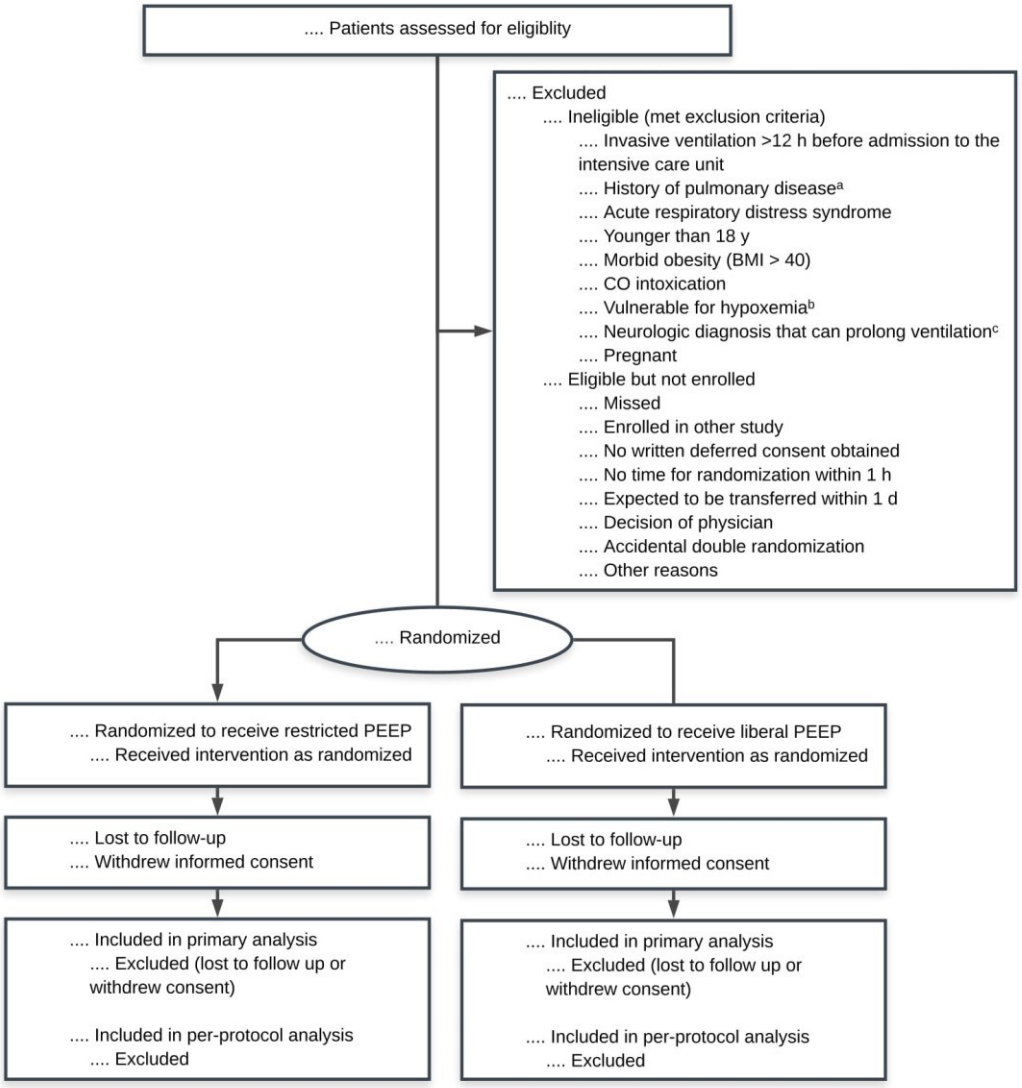
MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN (*Trials* 2018;19:272)	UPDATE IN THE SAP* (Closed in August 27, 2019)	IN THE PAPER	MODIFICATIONS *POST-HOC***
Primary outcome	Depending on the distribution a parametric or nonparametric analysis method	Mean ratio estimated using GAMLSS considering a zero-inflated beta distribution		
Secondary outcomes	ICU length of stay Hospital length of stay ICU mortality Hospital mortality 90-day mortality Development of ARDS Development of Pneumonia Development of Pneumothorax Development of Severe Atelectasis Development of Severe Hypoxemia Need for rescue strategies for severe hypoxemia or severe atelectasis (recruitment maneuver, prone positioning and/or bronchoscopy for opening atelectasis) Days with use of hemodynamic support Days with use of sedation	ICU length of stay Hospital length of stay Duration of ventilation in survivors ICU mortality Hospital mortality 28-day mortality 90-day mortality Development of new ARDS Development of Pneumothorax Development of suspected VAP Development of confirmed VAP Development of Severe Atelectasis Development of Severe Hypoxemia Need for rescue strategies for severe hypoxemia or severe atelectasis (recruitment maneuver, prone positioning and/or bronchoscopy for opening atelectasis) Days with use of hemodynamic support Days with use of sedation		
Additional analyses	Not planned	Duration of ventilation in survivors, and time until ICU and hospital discharge assessed in competing risk model Sensitivity analysis with mixed–effect or Cox models with stratifications variables		

		as random–effect with adjustment of covariates Generalized pairwise comparisons
Subgroup analyses	Obesity or not Pneumonia or not Ventilation parameters: tidal volume, respiratory rate, plateau pressure, pressure support	Obesity or not Surgical Admission or not Respiratory failure or not Cardiac Arrest or not PaO_2 / FiO_2 ratio According to LIPS According to SAPS
Statistical approach for subgroup analyses	Not described	Interaction effects between each subgroup and the study arms by GAMLSS considering zero–inflated distributions
Per protocol analyses	Only considers those patients who completed PEEP titrations according to the originally allocated treatment study protocol	Described according to protocol violations
Mock tables	Not included	Included
Other	Nothing	Competing risk model to asses duration of ventilation, time until ICU and hospital discharge with Fine-Gray model Mixed–effect or (shared-frailty) Cox proportional hazard models to re-estimate effect of intervention on primary and secondary outcomes

ICU: intensive care unit; ARDS: acute respiratory distress syndrome; VAP: ventilator-associated pneumonia; GAMLSS: generalized additive model for location scale and shape; LIPS: Lung Injury Prediction Score; SAPS: Simplified Acute Physiology Score;
* Database locking in Month Day, 2020
** Not considered neither in the original plan nor in the updated SAP

PROPOSED FIGURE 1



a Includes chronic obstructive pulmonary disease (COPD) stage III and IV in the GOLD classification, and restricitve pulmonary disease. COPD GOLD III is defined as severe obstruction of the airways with $FEV_1/FVC<70\%$, FEV_1 between 30% and 50% of predicted values. COPD GOLD IV is defined as very severe obstruction of the airways with $FEV_1/FVC < 70\%$, FEV_1 below 30% of predicted values

b Includes ongoing cardiac ischemia due to cardiac infarction and failed revascularization, uncontrollable intracranial pressure, delayed cerebral ischemia after subarachnoid hemorrhage, necrotizing fasciitis, and severe untreatable anemia such as Jehovah's Witnesses.

c Includes Guillain–Barré syndrome, high spinal cord lesion or amyotrophic lateral sclerosis, multiple sclerosis, or myasthenia gravis .

PROPOSED FIGURE 2 (SIMULATED DATA)