Updated and Finalized Statistical Analysis Plan of the 'PROtective Ventilation with Higher Versus Lower PEEP During One–lung Ventilation for THORacic Surgery' (PROTHOR) Randomized Clinical Trial

The PROTHOR–investigators

INTRODUCTION

The 'PROtective Ventilation with High versus Low PEEP during One–lung Ventilation for THORacic surgery' (PROTHOR) randomized clinical trial compares an intraoperative ventilation strategy with higher positive end–expiratory pressure (PEEP) with recruitment maneuvers ('higher PEEP') to a conventional strategy consisting of lower PEEP of 5 cmH_2O without recruitment maneuvers ('lower PEEP'), both with low tidal volumes.[1] The primary objective of this study is to determine whether 'higher PEEP' is superior to 'lower PEEP' with regard to the incidence of postoperative pulmonary complications (PPC). Enrollment of patients in the PROTHOR study is progressing well and the study is planned to enroll the last patient in the second trimester of 2024.

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 the PROTHOR study.

METHODS

Design, ethics and registration

The PROTHOR study is an international, multicenter, parallel, two–group, prospective, randomized, patient and outcome–assessor blinded superiority clinical trial designed to determine if an intra–operative higher PEEP strategy is superior to a lower PEEP strategy with respect to the development of PPC in adult patients submitted to thoracic surgery requiring one–lung ventilation (OLV).

The protocol, with a detailed description of the study population, the two strategies and follow–up plan of the PROTHOR trial were previously published elsewhere.[1] The PROTHOR study is registered at clinicaltrials.gov (study identifier NCT02963025) and was approved by the Ethical Committee of the Istanbul University, Medical Faculty, Turkey (2016/483, April 8, 2016). Additionally, the institutional review board at the University Hospital Dresden, Technische Universität Dresden, Dresden, Germany, approved the study on 23.09.2016 (reference no. EK 392092016). The respective review boards of participating sites approved the study as well.

Randomization and blinding

Eligible patients are randomly allocated in a 1:1 ratio to the ‘higher PEEP’ or ‘lower PEEP’ strategy. The allocation sequence is computer–generated by an independent investigator using permuted blocks of random size of four, six, and eight patients, and stratified per center. Randomization is performed by local investigators patient–by–patient employing a dedicated, password protected, SSL–encrypted website.

At each site, at least two investigators are involved with the study. One local investigator randomizes the patients immediately before surgery, and is

responsible for the trial intervention and data collection. A second local investigator remains blinded to the assigned treatment, and is responsible for postoperative data collection.

Outcomes

The primary study outcome is a collapsed composite of PPC developing within the first five postoperative days. This endpoint follows the European Perioperative Clinical Outcome (EPCO) definition and has been used before in several clinical trials.[2-4] A patient that develops one or more PPCs is considered as meeting the primary outcome. The components of the composite outcome of PPC have been defined and described elsewhere,[1] and include: 1) aspiration pneumonitis; 2) moderate respiratory failure; 3) severe respiratory failure; 4) acute respiratory distress syndrome (ARDS); 5) pulmonary infection; 6) atelectasis; 7) cardiopulmonary edema; 8) pleural effusion; 9) pneumothorax on the non-surgical lung; 10) pulmonary infiltrates; 11) prolonged air leakage; 12) purulent pleuritic; 13) pulmonary embolism; and 14) lung hemorrhage. The selected PPC can sensibly be merged as they share common pathophysiological mechanisms and have plausibility to be affected in the same direction by the intervention tested in this study.

Secondary outcomes include: 1) extended PPC, including bronchospasm or mild respiratory failure; 2) severe PPC, as defined in a recent published clinical trial[5] (composite of severe respiratory failure, pneumothorax, ARDS, pulmonary infection, prolonged air leakage, purulent pleuritis, new requirement of non-invasive or invasive ventilation due to respiratory failure and/or atelectasis); 3) a composite outcome of intraoperative complications, including use of continuous positive airway pressure for the non-ventilated lung, use of inhaled nitric

oxide/prostacycline, use of selective fiberoscope insufflation, hypotension unresponsive to fluids and/or vasoactive drugs, new arrhythmias unresponsive to intervention, need for high dosage of vasoactive drugs, need for massive transfusion, life-threatening surgical complication (including major bleeding, tension pneumothorax and intracranial injury), hypoxemia and hypercapnia rescue maneuvers; 4) postoperative extrapulmonary complications, including systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, extrapulmonary infection, coma, acute myocardial infarction, acute renal failure, disseminated intravascular coagulation, stroke, hepatic failure, and gastrointestinal failure; 5) need for unexpected intensive care unit admission or readmission; 6) any postoperative respiratory intervention used for respiratory failure (new requirement of non-invasive ventilation or mechanical ventilation); 7) number of hospital-free days at day 28; 8) in-hospital mortality; 9) 90-day mortality; 10) arterial blood gas analysis during surgery (PaO_2, $PaCO_2$, pHa). All definitions are available in **Table 1**.

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 fix missing data, 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 locking, the data will be exported for statistical analysis. At this stage, permission for access to the database will be removed for all investigators, and the database is 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 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

An adaptive trial design is used, which accumulates data and uses external information to modify aspects of the design without undermining the validity and integrity of the trial. The group sequential methods design offers the possibility for early stopping the study if the experimental treatment shows a statistically significant therapeutic advantage at an interim assessment, but also allows early stopping for futility if the interim analysis reveals that, with high probability, the trial will be negative.

PROTHOR is designed to enroll a total of 2378 patients (1189 in each arm). This number allows the detection of a reduction in the incidence of the primary outcome from 23% in the 'lower PEEP' group to 17.25% in the 'higher PEEP' group (relative risk reduction of 25%), considering a type I error of 5%, a power of 90%, similar allocation ratio between the arms (1:1) and a dropout rate of 5%. The required sample size is calculated based on an estimated effect size derived from individual patient data from previous trials,[3,4,6-9] and the LAS VEGAS study.[10]

An alpha–spending function was used to generate efficacy boundaries and a beta-spending function to generate futility boundaries (gamma family spending function, type I error 0.05, type II error 0.1). By using a gamma of −4 for the alpha

and gamma of −2 for the beta spending function a moderate hurdle for early stopping for efficacy and a reasonable chance to stop early due to futility is considered. A non-binding futility boundary was constructed in such a way that it can be overruled if desired without inflating the type 1 error. This flexibility is important, since the data monitoring committee might well prefer to keep the trial going to gather additional information, despite crossing the futility boundary (**Figure 1** and **Table 2**).

Interim analyses

Five interim assessments for evaluation of efficacy, harm, and/or futility were planned, with the aim of possibly stopping the study early. The planned number of assessments describes the number of time points, including the closing date of the study, at which the investigator plans to analyze the thus far collected data. The spacing of assessments will be equal. Therefore, interim analyses were performed after 20% (476 patients), 40% (952 patients), 60% (1426 patients), and 80% (1902 patients) of the planned inclusions, and the final analysis will be performed after 2378 patients (100%) are included (**Table 2**).

Statistical analyses

All statistical analyses will be conducted on an intention–to–treat basis, with patients analyzed 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. Variables will be expressed as counts and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR) whenever appropriate.

The study was designed to detect a difference in the primary outcome with 90% power, using a two–sided superiority hypothesis test with a significance level

of 0.0428 (correspondent to the Z-value of 2.025 for efficacy or futility in the final analysis in **Table 2**) and presented with a two–sided 95% confidence interval. Secondary outcomes will be assessed using a two–sided superiority hypothesis test with a significance level of 0.05 and presented with a two–sided 95% confidence interval. In addition to the unadjusted *p* values for secondary outcomes, a Holm–Bonferroni procedure will be applied to control for multiple testing.[11] Analyses will be performed using the software R (R Core Team, 2016, Vienna, Austria). A list of proposed tables and figures is in **Table 3**.

Trial profile

Patient flows will be represented in a CONSORT flowchart (**Proposed Inserts**).

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group (**Proposed Inserts**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Whenever 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 mean and standard deviation (SD) or median and interquartile range (IQR), according to the observed distribution of the variable.

Adherence to study protocol and ventilatory variables

Surgical and perioperative characteristics will be reported (**Proposed Inserts**). Ventilatory variables and vital signs will be reported after intubation, one hour, and in the last hour of surgery and compared between the two groups. Absolute differences between groups will be calculated using median regression for continuous variables (reported as median difference) and generalized linear

models with binomial distribution and an identity link for binary variables (reported as difference in percentages). Plots comparing ventilatory variables and vital signs among the groups during the first three hours of surgery and in the last hour will be drawn (presenting the data as mean and 95% confidence interval in each time point).

Other daily characteristics

Daily variables will be reported according to the description in **Proposed Inserts**. Absolute differences between groups will be calculated using median regression for continuous variables (reported as median difference) and generalized linear models with binomial distribution and an identity link for binary variables (reported as difference in percentages). Plots comparing daily variables among the groups will be constructed (presenting the data as mean and 95% confidence interval in each time point).

Primary outcome

The effect of 'higher PEEP' compared to 'lower PEEP' on the incidence of PPC will be assessed using a mixed–effect generalized linear model with binomial distribution and identity link, with sites included as random effects to account for the clustering effect and reported as absolute difference with a two–sided 95% confidence interval. Results will be presented in a table of outcomes (**Proposed Inserts**).

Secondary outcomes

For binary outcomes, the effect of 'higher PEEP' compared to 'lower PEEP' will be assessed using a mixed–effect generalized linear model with binomial distribution and identity link, with sites included as random effects to account for the clustering effect and reported as absolute difference with a two–sided 95%

confidence interval. For continuous outcomes, the comparison will be made using a mixed-effect median regression with sites also including as clustering effect, and reported as median difference with a two–sided 95% confidence interval. 90-day mortality will be assessed using Kaplan–Meier curves, and hazard ratios with 95% confidence intervals will be calculated with (shared-frailty) Cox proportional hazard models without adjustment for covariates and including sites as frailty. The proportional hazard assumptions will be tested using scaled Schoenfeld residuals 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–wise error rate to the *p* values for all secondary outcomes will be done and presented in a Table.

Per–protocol analysis

The per–protocol population will consist of patients truly ventilated according to the protocol. Thus, patients will be excluded from this population if receiving PEEP < 10 cm H_2O in the 'higher PEEP' group or PEEP > 5 cm H_2O and FiO_2 < 1.0 in the 'lower PEEP' group, unless rescue for hypoxemia or hypercapnia required adjustments of PEEP and F_iO_2 as defined by the protocol.

Subgroup analysis

Treatment effects on incidence of PPC will be analyzed according to the following predefined subgroups: 1) type of surgery (non–thoracoscopic versus thoracoscopic); 2) positioning (lateral decubitus versus supine position); 3) baseline SpO_2 < 96% versus SpO_2 ≥ 96%; 4) chronic obstructive pulmonary disease (COPD) versus non-COPD; 5) body mass index < 30 kg/m^2 versus ≥ 30 kg/m^2; and 6) duration of one-lung ventilation < 120 versus ≥ 120 minutes. Analyses of heterogeneity of effects across subgroups will be performed with the

use of treatment–by–subgroup term added to the primary model and will be presented in a forest plot.

Other exploratory analyses

Given that the primary outcome of the present study is a collapsed composite, the choice of the statistical method is an important part of designing since various methods provide different power, depending on the situation. In addition to the standard analysis described above, the following analyses will be performed:

- Count analysis: the number of positive component events (i.e., 'count') across the composite will be assessed. The groups will be compared on the count using a Wilcoxon rank sum test, and the odds ratio with the 95% confidence interval will be assessed with a cumulative logistic regression model;
- Individual component analysis: the effect of the intervention in each component will be analyzed estimating the risk ratio and confidence intervals with Wald's likelihood ratio approximation test using a Bonferroni correction for multiple comparisons. The 99.6% Bonferroni–corrected confidence intervals will be reported (1 – 0.05/14 = 0.996);
- Common effect test: A multivariate (i.e., multiple outcomes per subject) generalized estimating equations (GEE) model will be used to estimate a common effect odds ratio across the components;
- Average relative effect test: The average relative effect test will be assessed by averaging the component-specific treatment effect from the distinct effects model, and testing whether the average is equal to zero. In the GEE distinct effect model a distinct treatment effect is estimated for each component; and

- Heterogeneity of treatment effect: Heterogeneity of treatment effect across components will be assessed by a treatment-by-component interaction test in the distinct effects GEE model.

REFERENCES

1. Kiss T, Wittenstein J, Becker C, et al. Protective ventilation with high versus low positive end-expiratory pressure during one-lung ventilation for thoracic surgery (PROTHOR): study protocol for a randomized controlled trial. Trials 2019;20:213.

2. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015;32:88–105.

3. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz M. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014;384:495–503.

4. Ferrando C, Soro M, Unzueta C, et al. Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial. Lancet Respir Med 2018;6:193–203.

5. Ferrando C, Carramiñana A, Piñeiro P, et al. Individualised, perioperative open-lung ventilation strategy during one-lung ventilation (iPROVE-OLV): a multicentre, randomised, controlled clinical trial. Lancet Respir Med 2023;[in press].

6. Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013;369:428–37.

7. Ge Y, Yuan L, Jiang X, Wang X, Xu R, Ma W. Effect of lung protection mechanical ventilation on respiratory function in the elderly undergoing spinal fusion. J Cent South Univ 2013;38:81–5.

8. Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology 2013;118:1307–21.

9. Ferrando C, Soro M, Unzueta C, et al. Rationale and study design for an individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) and its effects on surgical site infection: study protocol for a randomised controlled trial. BMJ Open 2017;7:e016765.

10. LAS VEGAS Investigators. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - an observational study in 29 countries. Eur J Anaesthesiol 2017; 34:492–507.

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

Table 1 – Definitions of Outcomes

Outcomes	Definition
Aspiration pneumonitis	Respiratory failure after the inhalation of regurgitated gastric contents.
Moderate respiratory failure	SpO_2 < 90% or PaO_2 < 60 mmHg for 10 min in room air, responding to oxygen > 2 L/min.
Severe respiratory failure	Need for noninvasive or invasive mechanical ventilation due to poor oxygenation.
Acute respiratory distress syndrome	According to the Berlin criteria for acute respiratory distress syndrome*.
Pulmonary infection	Defined as new or progressive radiographic infiltrate plus at least two of the following: • Antibiotic treatment; • Tympanic temperature > 38 °C; • Leukocytosis or leucopenia (white blood cell count < 4000 cells/mm3 or > 12,000 cells/mm3); • Purulent secretions
Atelectasis	Lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung.
Cardiopulmonary edema	Clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest radiograph demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates.
Pleural effusion	Chest x-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows.
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiography.
Pulmonary infiltrates	Chest x-ray demonstrating new unilateral or bilateral infiltrate without other clinical signs.
Prolonged air leakage	Air leak requiring at least 7 days of postoperative chest tube drainage.
Purulent pleuritic	Receiving antibiotics for a suspected infection, as far as not explained by the preoperative patient condition alone.
Pulmonary embolism	As documented by pulmonary arteriogram or autopsy, or supported by ventilation/perfusion radioisotope scans, or documented by echocardiography and receiving specific therapy.
Lung hemorrhage	Bleeding through the chest tubes requiring reoperation, or three or more red blood cell packs.
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators.
Mild respiratory failure	PaO_2 < 60mmHg (or < 7.9 kPa) or SpO_2 < 90% for 10 minutes in room air, but responding to oxygen ≤ 2 L/min.
Systemic inflammatory response syndrome	Presence of two or more of the following: • Body temperature < 36 °C or > 38 °C; • Heart rate > 90 beats per minute; • Respiratory rate > 20 breaths per minute or, on blood gas, a $PaCO_2$ < 32 mmHg (4.3 kPa); • White blood cell count < 4000 cells/mm3 or > 12,000 cells/mm3, or > 10% band forms.
Sepsis	Systemic inflammatory response syndrome in response to a confirmed infectious process; infection can be suspected or proven (by culture, stain, or polymerase

	chain reaction), or a clinical syndrome pathognomonic for infection
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion, or hypotension), septic shock (sepsis with refractory arterial hypotension or hypoperfusion abnormalities in spite of adequate fluid resuscitation); signs of systemic hypoperfusion may be either end-organ dysfunction or serum lactate greater than 4 mmol/dL, other signs include oliguria and altered mental status.
Septic shock	Sepsis plus hypotension after aggressive fluid resuscitation, typically upwards of 6 L or 40 mL/kg of crystalloid.
Extrapulmonary infection	Wound infection + any other infection.
Coma	Glasgow Coma Score < 8 in the absence of therapeutic coma or sedation.
Acute myocardial infarction	Detection of rise and/or fall of cardiac markers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with symptoms of ischemia, electrocardiography changes indicative of new ischemia, development of pathological Q-waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or sudden unexpected cardiac death, involving cardiac arrest with symptoms suggestive of cardiac ischemia (but death occurring before the appearance of cardiac markers in blood).
Acute renal failure	Documented as follows: • Risk: increased creatinine × 1.5 or glomerular filtration rate (GFR) decrease > 25% or urine output (UO) < 0.5 mL/kg/h × 6 h; • Injury: increased creatinine × 2 or GFR decrease > 50% or UO < 0.5 mL/kg/h × 12 h; • Failure: increased creatinine × 3 or GFR decrease > 75% or UO < 0.3 mL/kg/h × 24 h or anuria × 12 h; • Loss: persistent acute renal failure = complete loss of kidney function > 4 weeks.
Disseminated intravascular coagulation	Documented as follows: • Platelet count < 50 (2 points), < 100 (1 point), or ≥ 100 (0 points); • D-dimer > 4 µg/mL (2 points), > 0.39 µg/mL (1 point) or ≤ 0.39 µg/mL (0 points); • Prothrombin time > 20.5 s (2 points), > 17.5 s (1 point), or ≤ 17.5 s (0 points). If ≥ 5 points: overt disseminated intravascular coagulation
Stroke	New clinical signs of stroke lasting longer than 24 h and corresponding findings in radiologic imaging
Hepatic failure	Hepatic failure during short-term follow-up (5 postoperative days) is considered as follows: • Bilirubin serum level > 2 mg/dL; • Elevation of alanine amino transferase/aspartate amino transferase; • Lactate dehydrogenase × 2 above normal values. During long-term follow-up (until postoperative day 90): • New presence of hepatic encephalopathy; • Coagulopathy (international normalized ratio (INR) > 1.5) within 8 weeks after initial signs of liver injury (e.g., jaundice) without evidence for chronic liver disease.

Gastrointestinal failure	Any type of gastrointestinal bleeding or gastrointestinal failure score documented as follows: • 0 = normal gastrointestinal function; • 1 = enteral feeding with under 50% of calculated needs or no feeding 3 days after abdominal surgery; • 2 = food intolerance or intraabdominal hypertension; • 3 = food intolerance and intra-abdominal hypertension; and • 4 = abdominal compartment syndrome
Number of hospital-free days at day 28	Defined as the number of days that a patient was not in hospital nor rehabilitation or nursing facility at day 28 after randomization. Hospital readmission is only counted if the patient stays overnight (= 2 days). Patients who die or have longer length of stay than 28 days are assigned zero hospital free days.

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

Table 2 – Z-statistic Boundaries and Boundary Crossing Probabilities

Look	Information Fraction	*N*	Cumulative α spent	Cumulative β spent	Z-efficacy/harm	Z-futility	Boundary crossing probabilities under H_1	
							Efficacy	Futility
1	0.20	452	0.001	0.008	± 3.252	± 0.031	0.042	0.008
2	0.40	904	0.004	0.019	± 2.986	± 0.152	0.170	0.011
3	0.60	1355	0.009	0.036	± 2.692	± 0.631	0.281	0.017
4	0.80	1807	0.022	0.062	± 2.374	± 1.344	0.263	0.026
5	1.00	2259	0.050	0.100	± 2.025	± 2.025	0.143	0.038

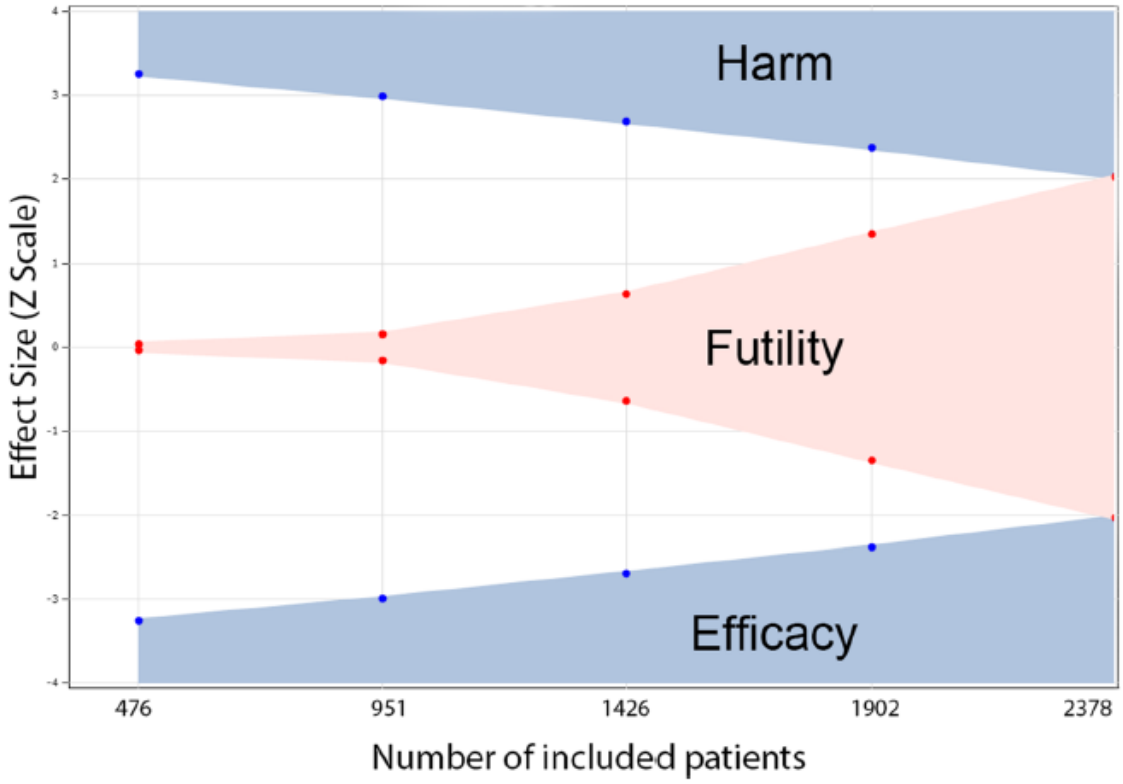
Values were calculated using power = 0.90, alpha = 0.05, gamma spending function − 4 for the alpha and − 2 for the beta, expected incidence of postoperative pulmonary complications of 23% and 17.25% in the lower and higher positive end-expiratory pressure groups, respectively. Number of patients (N) is shown without correcting for dropouts. Look, interim analysis; H1, hypothesis 1 (group difference exists).

Table 3 – List of proposed tables and figures

	Description
Main paper	
Table 1	Baseline Characteristics of the Included Patients
Table 2	Ventilation and Intraoperative Characteristics
Table 3	Primary and Secondary Outcomes
Figure 1	Participant Flow Diagram
Figure 2	Postoperative Pulmonary Complications in Prespecified Subgroups *A forest plot showing the absolute difference and two–sided 95% confidence intervals with p value for interaction calculated via a test for treatment–by–subgroup interaction in the regression 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	Rate of Missing Data *A table showing the rate of missing data.*
eTable 2	Additional Baseline Characteristics *A table showing additional baseline characteristics.*
eTable 3	Additional Intraoperative Characteristics *A table showing additional intraoperative characteristics.*
eTable 4	Intraoperative Fluid and Drug Therapy *A table reporting intraoperative fluid and drug therapy each arm.*
eTable 5	Protocol Deviations *A table describing protocol deviations.*
eTable 6	Daily Assessment of Included Patients *A table describing daily assessment of patients.*
eTable 7	Additional Daily Assessment of Included Patients *A table describing daily assessment of patients.*
eTable 8	Daily Signs and Laboratory of Included Patients *A table describing daily assessment of patients.*
eTable 9	Day 1 Fluid and Drug Therapy *A table reporting day 1 fluid and drug therapy each arm.*
eTable 10	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*
eTable 11	Sensitivity Analyses for the Primary Outcome *A table showing the proposed sensitivity analyses for the primary outcome (count analysis, common effect test, average relative effect test and heterogeneity of treatment effect)*
eFigure 1	Tidal Volume, PEEP, Peak Pressure, Plateau Pressure, Driving Pressure and FiO_2 During Surgery *Line graph reporting the mean and 95% confidence interval of the variables at induction, final positioning with two lung ventilation, 10 minutes of one lung ventilation and at the end of surgery by treatment group.*
eFigure 2	VAS Dyspnea, VAS Thoracic Pain, VAS Coughing Pain, Respiratory Rate, SpO_2 and Mean Arterial Pressure During the First Five Days of Follow-Up *Line graph reporting the mean and 95% confidence interval of the variables in the first five days of follow-up by treatment group.*

eFigure 3	Results of the Sensitivity Analyses for the Primary Outcome *Forest plot reporting the results of all sensitivity analyses*

Figure 1 – PROTHOR Adaptive Design



Effect size (Z) according to enrollment of patients in the PROTHOR trial (including dropouts). Values of Z were from an adaptive sequential design (see text) with stopping criteria for harm, futility, and efficacy of the intervention.

MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN (*TRIALS* 2019; 20:213)	UPDATE IN THE SAP* (Closed in January 17th, 2024)
Definition of intraoperative complications (secondary outcome)	Included 'deviation from prescribed PEEP or tidal volume' in the definition	'deviation from prescribed PEEP or tidal volume' removed from the definition
Requirement of postoperative respiratory intervention (secondary outcome)	Any requirement of postoperative respiratory intervention	Requirement of postoperative respiratory intervention for respiratory failure only (excludes for reoperation)
Secondary outcome	---	Addition of severe postoperative pulmonary complications.
Model for the primary outcome	Risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.	Mixed-effect generalized linear model with binomial distribution and identity link, with sites included as random effects to account for the clustering effect and reported as absolute difference with a two-sided 95% confidence interval.
Model for binary secondary outcomes	Risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.	Mixed-effect generalized linear model with binomial distribution and identity link, with sites included as random effects to account for the clustering effect and reported as absolute difference with a two-sided 95% confidence interval.
Model for hospital-free days at day 28	Student *t* test and reported as the mean difference between the two groups. The consistency of the findings of the Student *t* test will be confirmed according to the mean ratio calculated by a generalized additive model considering a zero-inflated beta distribution.	Mixed-effect median regression with sites also including as clustering effect, and reported as median difference with a two-sided 95% confidence interval.
Time-to-event analyses for PPC	Kaplan–Meier curves will be used to report time to postoperative pulmonary complications, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates.	No time-to-event analysis planned to be performed for PPC.
Time-to-event analyses for 90-day mortality	Hazard ratios with 95% confidence intervals will be calculated with Cox proportional hazard models without adjustment for covariates and including sites as frailty.	Hazard ratios with 95% confidence intervals will be calculated with (shared-frailty) Cox proportional hazard models without adjustment for covariates and including sites as frailty.
Subgroup analysis (definition)	---	Added two additional subgroups: body mass index and duration of one-lung ventilation.
Subgroup analysis (method)	The effects on subgroups will be evaluated according to the interaction effects between each subgroup and the study arms by generalized linear models and presented in a forest plot.	Analyses of heterogeneity of effects across subgroups will be performed with the use of treatment-by-subgroup term added to the primary model and will be presented in a forest plot.

LIST OF PROPOSED INSERTS

Table 1 – Baseline Characteristics of the Included Patients

	Higher PEEP (*n* =)	Lower PEEP (*n* =)
Age, years		
Age ≥ 65 years – no. (%)		
Female gender – no. (%)		
Body mass index, kg/m^2		
Body mass index ≥ 30 kg/m^2		
ARISCAT score		
ARISCAT ≥ 45 – no. (%)		
ASA physical status– no. (%)		
1		
2		
3		
4		
Priority of surgery – no. (%)		
Elective		
Urgent		
Emergency		
Surgical procedure – no. (%)		
Thoracoscopic		
Open		
Converted from thoracoscopic to open		
Cumulated ambulation score		
Co-existing disorders – no. (%)		
Hypertension		
Heart failure		
Coronary artery disease		
Diabetes		
Obstructive sleep apnea		
Chronic obstructive pulmonary disease		
Use of noninvasive ventilation		
Active cancer		
Respiratory infection within last month		
Smoking status		
Never		
Former (cessation > 3 months)		
Current		
Alcohol (> 2 drinks/day)		
Preoperative signs		
SpO_2, %		
Respiratory rate, breaths/min		
Heart rate, beats per minute		
Mean arterial blood pressure, mmHg		

Data are median (quartile 25th - quartile 75th) or N / total (%).
Abbreviations: PEEP is positive end-expiratory pressure; ARISCAT is The Assess Respiratory Risk in Surgical Patients in Catalonia; ASA is American Society of Anesthesiology; SpO_2 is pulse oximetry.

Table 2 – Ventilation and Intraoperative Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Recruitment maneuver – no. (%)				
Number of recruitment maneuvers				
Tidal volume, mL/kg PBW				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
PEEP, cmH_2O				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
Peak pressure, cmH_2O				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
Plateau pressure, cmH_2O				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
Driving pressure, cmH_2O				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
Respiratory rate, breaths/min				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
FiO_2				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
SpO_2, %				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				

Table 2 – Ventilation and Intraoperative Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
$etCO_2$, mmHg				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
Mean arterial pressure, mmHg				
Induction				
Final position with two lung ventilation				
10 minutes after one lung ventilation				
End of surgery, supine, two lung ventilation				
Duration of anesthesia, min				
Duration of one lung ventilation, min				
Duration of two lung ventilation, min				
Duration of surgery, min				
Duration of surgery ≥ 180 min – no. (%)				
Fluids				
Total intake, mL				
Fluid balance, mL				

Data are median (quartile 25th - quartile 75th) or N / total (%).

Abbreviation: PEEP is positive end-expiratory pressure; PBW is predicted body weight; FiO_2 is inspired fraction of oxygen; SpO_2 is pulse oximetry; $etCO_2$ is end-tidal carbon dioxide.

Table 3 – Primary and Secondary outcomes

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Primary outcome				
Postoperative pulmonary complications – no. (%)				
Aspiration pneumonitis				
Moderate respiratory failure				
Severe respiratory failure				
Acute respiratory distress syndrome				
Pulmonary infection				
Atelectasis				
Cardiopulmonary edema				
Pleural effusion				
Pneumothorax				
Pulmonary infiltrates				
Prolonged air leakage				
Purulent pleuritic				
Pulmonary embolism				
Lung hemorrhage				
Secondary outcomes				
Extended postoperative pulmonary complications – no. (%)				
Mild respiratory failure				
Bronchospasm				
Intraoperative complications – no. (%)				
CPAP for the non-ventilated lung				
iNO, prostacycline or selective fiberoscope insufflation				
Hypotension unresponsive to fluids or vasoactive drugs				
New arrhythmias unresponsive to intervention				

Need for high dosage of vasoactive drugs
Need for massive transfusion
Life-threatening surgical complication*
Hypoxemia rescue maneuvers
Hypercapnia rescue maneuvers
Postoperative extrapulmonary complications – no. (%)
Systemic inflammatory response syndrome
Sepsis
Severe sepsis
Septic shock
Extrapulmonary infection
Coma
Acute myocardial infarction
Acute renal failure
Disseminated intravascular coagulation
Stroke
Hepatic failure
Gastrointestinal failure
Unexpected ICU admission or readmission – no. (%)
Postoperative respiratory intervention – no. (%)
Non-invasive ventilation
Invasive ventilation
Number of hospital-free days at day 28
All-cause hospital mortality – no. (%)
90-day mortality – no. (%)

Data are median (quartile 25th - quartile 75th) or N / total (%).
Abbreviations: PEEP is positive end-expiratory pressure; CPAP is continuous positive airway pressure; iNO is inhaled nitric oxide; ICU is intensive care unit.
* Including major bleeding, tension pneumothorax and intracranial injury.

eTable 2 – Additional Baseline Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)
Cumulated ambulation score		
Transfer from supine-to-sitting-to-supine – no. (%)		
Unable to perform function despite assistance from 2 people		
Only able to perform function with assistance from 1 or 2 people		
Able to perform function independently		
Transfer from sitting-to-standing-to-sitting (from armchair) – no. (%)		
Unable to perform function despite assistance from 2 people		
Only able to perform function with assistance from 1 or 2 people		
Able to perform function independently		
Walking (with appropriate walking aid) – no. (%)		
Unable to perform function despite assistance from 2 people		
Only able to perform function with assistance from 1 or 2 people		
Able to perform function independently		
≥ 4 metabolic equivalents		
Co-existing disorders		
Heart failure – no. (%)		
NYHA score		
1		
2		
3		
4		
Coronary artery disease – no. (%)		
CCS score		
Atrial flutter / fibrillation – no. (%)		
Acute		
Paroxysmal		
Chronic		
Diabetes – no. (%)		
Dietary		
Oral medication		
Insulin		
Obstructive sleep apnea – no. (%)		
Apnea/Hypopnea Index (events / hour)		
STOP BANG Score		
Chronic obstructive pulmonary disease – no. (%)		
Steroids use		
Inhalation therapy		
Use of noninvasive ventilation		
Continuous positive airway pressure		
Intensity of support (pressure level, cmH_2O)		

eTable 2 – Additional Baseline Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)
Duration (hours / day)		
Gastroesophageal reflux – no. (%)		
≥ 1 event/day		
≥ 1 event/week		
≥ 1 event/month		
Respiratory infection within last month – no. (%)		
Lower respiratory infection		
Medications – no. (%)		
Use of antibiotics (last 3 months)		
Use of statins		
Use of aspirin		
Preoperative signs		
FiO_2, %		
Temperature, ºC		
Tympanic – no. (%)		
Nasal/oral – no. (%)		
Bladder – no. (%)		
Other		
Preoperative laboratory tests		
Blood gas obtained – no. (%)		
Arterial – no. (%)		
pH		
PaO_2, mmHg		
$PaCO_2$, mmHg		
Hemoglobin, g/dL		
INR		
Creatinine, mg/dL		
BUN, mg/dL		
ALT, U		
AST, U		
Bilirubin, mg/dL		
C-reactive protein, mg/L		
Airway secretion – no. (%)		
VAS dyspnea		
VAS thoracic rest pain		
VAS coughing pain		
Spirometry obtained – no. (%)		
Forced vital capacity, L		
Predicted postoperative forced vital capacity, %		
Forced expiratory volume at 1 second, L/1 sec		

eTable 2 – Additional Baseline Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)
Predicted postoperative forced expiratory volume at 1 second, %		
Forced expiratory volume at 1 second / Forced vital capacity, %		
Total lung capacity, L		
Diffusing capacity for carbon monoxide		
mmol/min/kPa		
ml/min/mmHg		
Predicted postoperative diffusing capacity for carbon monoxide, %		
VO_2max (maximal oxygen consumption), mL/kg/min		
Preoperative chest X-ray – no. (%)		
Pulmonary infiltrates		
Pleural effusion		
Atelectasis		
Pneumothorax		
Cardiopulmonary edema		

Data are median (quartile 25th - quartile 75th) or N / total (%).

Abbreviations: PEEP is positive end-expiratory pressure; NYHA is New York Heart Association; INR is international normalized ratio; BUN is blood urea nitrogen; ALT is alanine transaminase; AST is aspartate transaminase; VAS is visual analogue scale.

eTable 3 – Additional Intraoperative Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Patient position during induction – no. (%)				
0 – 15º				
15 - 30º				
30 - 45º				
> 45º				
Use of NIV for induction – no. (%)				
Continuous positive airway pressure				
NPPV				
Method of one lung ventilation – no. (%)				
Double lumen tube				
Endobronchial blocker				
Double lumen tube (embedded camera)				
Other				
Confirmation of OLV – no. (%)				
Fiberoptic bronchoscopy				
Embedded camera				
Other				
Patient positioning during surgery – no. (%)				
Supine				
Lateral				
Prone				
Other				
Side of one lung ventilation – no. (%)				
Left				
Right				
Side of surgery – no. (%)				
Left				
Right				
Type of resection – no. (%)				
Pneumectomy				
Lobectomy				
Wedge resection				
Sleeve lobectomy				
Segment resection				
Pleurectomy				
Other				
Regional anesthesia				
Epidural				
Paravertebral				
Other				

eTable 3 – Additional Intraoperative Characteristics

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Neuromuscular monitoring – no. (%)				
Surgical wound classification – no. (%)				
Clean				
Clean-contaminated				
Contaminated				
Dirty				
Temperature at the end of the surgery, ºC				
Tympanic				
Nasal/oral				
Bladder				
Other				
Paralysis reversed				
Residual curarization				
Blood loss, mL				
Urine output, mL				
Continuation of ventilation – no. (%)				
Reason				
Hypothermia				
Bleeding				
Cardiovascular				
Respiratory failure				
Other				
Duration, hours				
Use of antibiotics – no. (%)				
Prophylaxis				
Therapeutic				

Data are median (quartile 25th - quartile 75th) or N / total (%).

Abbreviations: PEEP is positive end-expiratory pressure; NIV is non-invasive ventilation; NPPV is non-invasive positive pressure ventilation; OLV is one lung ventilation.

eTable 4 – Intraoperative Fluid and Drug Therapy

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Analgesia				
Alfentanyl – no. (%)				
Dose, mg				
Fentanyl – no. (%)				
Dose, mg				
Remifentanil – no. (%)				
Dose, mg				
Sufentanil – no. (%)				
Dose, mg				
Morphine – no. (%)				
Dose, mg				
Ketamine – no. (%)				
Dose, mg				
Volatiles				
Desflurane – no. (%)				
Dose, vol%*min				
Sevoflurane – no. (%)				
Dose, vol%*min				
Sedatives				
Dexmedetomidine – no. (%)				
Dose, mg				
Midazolam – no. (%)				
Dose, mg				
Propofol – no. (%)				
Dose, mg				
Thiopental – no. (%)				
Dose, mg				
Neuromuscular blocking agents				
Atracurium – no. (%)				
Dose, mg				
Cisatracurium – no. (%)				
Dose, mg				
Rocuronium – no. (%)				
Dose, mg				
Succinylcholine – no. (%)				
Dose, mg				
Vecuronium – no. (%)				
Dose, mg				
Fluids				
Hydroxyethyl starch – no. (%)				
Dose, mL				
Gelatine – no. (%)				

eTable 4 – Intraoperative Fluid and Drug Therapy

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Dose, mL				
Crystalloids – no. (%)				
Dose, mL				
Albumin – no. (%)				
Dose, mL				
Vasopressors				
Ephedrine – no. (%)				
Dose, mg				
Adrenaline – no. (%)				
Dose, mg				
Noradrenaline – no. (%)				
Dose, mg				
Phenylephrine – no. (%)				
Dose, mg				
Blood products				
Packed red blood cells – no. (%)				
Dose, mL				
Fresh frozen plasma – no. (%)				
Dose, mL				
Platelets – no. (%)				
Dose, mL				

Data are median (quartile 25th - quartile 75th) or N / total (%).
Abbreviations: PEEP is positive end-expiratory pressure.

eTable 5 – Protocol Deviations

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	*p* value
Any protocol deviation – no. (%)			
SBP < 90mmHg unresponsive to fluids and/or vasoactive drugs			
New arrhythmias unresponsive to intervention (according to ACLS)			
Dosage of vasoactive drugs at the tolerance limit of the physician			
Need for massive transfusion			
Life-threatening surgical complication*			
Hypoxemia rescue**			
Hypercapnia rescue***			
Deviation from prescribed PEEP			
Deviation from tidal volume			
Other			

Data are median (quartile 25th - quartile 75th) or N / total (%).

Abbreviations: PEEP is positive end-expiratory pressure.

* Injury to the hemodynamic and respiratory system and brain, including major bleeding, tension pneumothorax, intracranial injury.

** Other than prescribed was necessary due to prolonged SpO2< 90%.

*** Other than prescribed was necessary due to respiratory acidosis pH< 7.20

eTable 6 – Daily Assessment of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Day 1				
Still in hospital – no. (%)				
Unplanned ICU admission – no. (%)				
New requirement of NIV or IMV – no. (%)				
New requirement of NIV – no. (%)				
Indication – no. (%)				
Standard of care				
Respiratory failure				
Other				
Type – no. (%)				
CPAP				
NPPV				
Other				
Pressure level, cmH_2O				
Duration, hours				
New requirement of IMV – no. (%)				
Indication – no. (%)				
Resurgery				
Respiratory failure				
Other				
Duration, hours				
Physiotherapy – no. (%)				
Breathing exercises – no. (%)				
Incentive spirometry – no. (%)				
Cumulated ambulation score				
Day 2				
Still in hospital – no. (%)				
Unplanned ICU admission – no. (%)				
New requirement of NIV or IMV – no. (%)				
New requirement of NIV – no. (%)				
Indication – no. (%)				
Standard of care				
Respiratory failure				
Other				
Type – no. (%)				
CPAP				
NPPV				
Other				
Pressure level, cmH_2O				
Duration, hours				
New requirement of IMV – no. (%)				
Indication – no. (%)				
Resurgery				

eTable 6 – Daily Assessment of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Respiratory failure				
Other				
Duration, hours				
Physiotherapy – no. (%)				
Breathing exercises – no. (%)				
Incentive spirometry – no. (%)				
Cumulated ambulation score				
Day 3				
Still in hospital – no. (%)				
Unplanned ICU admission – no. (%)				
New requirement of NIV or IMV – no. (%)				
New requirement of NIV – no. (%)				
Indication – no. (%)				
Standard of care				
Respiratory failure				
Other				
Type – no. (%)				
CPAP				
NPPV				
Other				
Pressure level, cmH_2O				
Duration, hours				
New requirement of IMV – no. (%)				
Indication – no. (%)				
Resurgery				
Respiratory failure				
Other				
Duration, hours				
Physiotherapy – no. (%)				
Breathing exercises – no. (%)				
Incentive spirometry – no. (%)				
Cumulated ambulation score				
Day 4				
Still in hospital – no. (%)				
Unplanned ICU admission – no. (%)				
New requirement of NIV or IMV – no. (%)				
New requirement of NIV – no. (%)				
Indication – no. (%)				
Standard of care				
Respiratory failure				
Other				
Type – no. (%)				
CPAP				

eTable 6 – Daily Assessment of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
NPPV				
Other				
Pressure level, cmH_2O				
Duration, hours				
New requirement of IMV – no. (%)				
Indication – no. (%)				
Resurgery				
Respiratory failure				
Other				
Duration, hours				
Physiotherapy – no. (%)				
Breathing exercises – no. (%)				
Incentive spirometry – no. (%)				
Cumulated ambulation score				
Day 5				
Still in hospital – no. (%)				
Unplanned ICU admission – no. (%)				
New requirement of NIV or IMV – no. (%)				
New requirement of NIV – no. (%)				
Indication – no. (%)				
Standard of care				
Respiratory failure				
Other				
Type – no. (%)				
CPAP				
NPPV				
Other				
Pressure level, cmH_2O				
Duration, hours				
New requirement of IMV – no. (%)				
Indication – no. (%)				
Resurgery				
Respiratory failure				
Other				
Duration, hours				
Physiotherapy – no. (%)				
Breathing exercises – no. (%)				
Incentive spirometry – no. (%)				
Cumulated ambulation score				

Data are median (quartile 25th - quartile 75th) or N / total (%).

Abbreviations: PEEP is positive end-expiratory pressure; ICU is intensive care unit; NIV is non-invasive ventilation; IMV is invasive mechanical ventilation; CPAP is continuous positive airway pressure; NPPV is non-invasive positive pressure ventilation

eTable 7 – Additional Daily Assessment of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Day 1				
Impairment of wound healing – no. (%)				
Superficial				
Deep				
Surgical wound infection – no. (%)				
Superficial				
Deep				
Antibiotics – no. (%)				
Therapeutically				
PONV – no. (%)				
Return of bowel function – no. (%)				
Airway secretion – no. (%)				
Purulent/yellow color				
Not purulent				
VAS dyspnea				
VAS thoracic pain				
VAS coughing pain				
Day 2				
Impairment of wound healing – no. (%)				
Superficial				
Deep				
Surgical wound infection – no. (%)				
Superficial				
Deep				
Antibiotics – no. (%)				
Therapeutically				
PONV – no. (%)				
Return of bowel function – no. (%)				
Airway secretion – no. (%)				
Purulent/yellow color				
Not purulent				
VAS dyspnea				
VAS thoracic pain				
VAS coughing pain				
Day 3				
Impairment of wound healing – no. (%)				
Superficial				
Deep				
Surgical wound infection – no. (%)				
Superficial				
Deep				
Antibiotics – no. (%)				
Therapeutically				
PONV – no. (%)				
Return of bowel function – no. (%)				

eTable 7 – Additional Daily Assessment of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Airway secretion – no. (%)				
Purulent/yellow color				
Not purulent				
VAS dyspnea				
VAS thoracic pain				
VAS coughing pain				
Day 4				
Impairment of wound healing – no. (%)				
Superficial				
Deep				
Surgical wound infection – no. (%)				
Superficial				
Deep				
Antibiotics – no. (%)				
Therapeutically				
PONV – no. (%)				
Return of bowel function – no. (%)				
Airway secretion – no. (%)				
Purulent/yellow color				
Not purulent				
VAS dyspnea				
VAS thoracic pain				
VAS coughing pain				
Day 5				
Impairment of wound healing – no. (%)				
Superficial				
Deep				
Surgical wound infection – no. (%)				
Superficial				
Deep				
Antibiotics – no. (%)				
Therapeutically				
PONV – no. (%)				
Return of bowel function – no. (%)				
Airway secretion – no. (%)				
Purulent/yellow color				
Not purulent				
VAS dyspnea				
VAS thoracic pain				
VAS coughing pain				

Data are median (quartile 25th - quartile 75th) or N / total (%).
Abbreviations: PEEP is positive end-expiratory pressure; PONV is postoperative nausea and vomiting; VAS is visual analogue scale.

eTable 8 – Daily Signs and Laboratory of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Day 1				
Respiratory rate, breaths/min				
Heart rate, bpm				
Mean arterial pressure, mmHg				
Temperature, ºC				
Tympanic				
Nasal/oral				
Bladder				
Other				
SpO_2, %				
FiO_2, %				
Hemoglobin, g/dL				
Creatinine, mg/dL				
Blood urea nitrogen, mg/dL				
ALT, U				
AST, U				
Bilirubin, mg/dL				
INR				
C-reactive protein, g/L				
Day 2				
Respiratory rate, breaths/min				
Heart rate, bpm				
Mean arterial pressure, mmHg				
Temperature, ºC				
Tympanic				
Nasal/oral				
Bladder				
Other				
SpO_2, %				
FiO_2, %				
Hemoglobin, g/dL				
Creatinine, mg/dL				
Blood urea nitrogen, mg/dL				
ALT, U				
AST, U				
Bilirubin, mg/dL				
INR				
C-reactive protein, g/L				
Day 3				
Respiratory rate, breaths/min				
Heart rate, bpm				
Mean arterial pressure, mmHg				
Temperature, ºC				
Tympanic				
Nasal/oral				

eTable 8 – Daily Signs and Laboratory of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Bladder				
Other				
SpO_2, %				
FiO_2, %				
Hemoglobin, g/dL				
Creatinine, mg/dL				
Blood urea nitrogen, mg/dL				
ALT, U				
AST, U				
Bilirubin, mg/dL				
INR				
C-reactive protein, g/L				
Day 4				
Respiratory rate, breaths/min				
Heart rate, bpm				
Mean arterial pressure, mmHg				
Temperature, ºC				
Tympanic				
Nasal/oral				
Bladder				
Other				
SpO_2, %				
FiO_2, %				
Hemoglobin, g/dL				
Creatinine, mg/dL				
Blood urea nitrogen, mg/dL				
ALT, U				
AST, U				
Bilirubin, mg/dL				
INR				
C-reactive protein, g/L				
Day 5				
Respiratory rate, breaths/min				
Heart rate, bpm				
Mean arterial pressure, mmHg				
Temperature, ºC				
Tympanic				
Nasal/oral				
Bladder				
Other				
SpO_2, %				
FiO_2, %				
Hemoglobin, g/dL				
Creatinine, mg/dL				
Blood urea nitrogen, mg/dL				

eTable 8 – Daily Signs and Laboratory of Included Patients

	Higher PEEP (*n* = XXX)	Lower PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
ALT, U				
AST, U				
Bilirubin, mg/dL				
INR				
C-reactive protein, g/L				

Data are median (quartile 25th - quartile 75th) or N / total (%).
Abbreviations: PEEP is positive end-expiratory pressure; INR is international normalized ratio; BUN is blood urea nitrogen; ALT is alanine transaminase; AST is aspartate transaminase.

eTable 9 – Day 1 Fluid and Drug Therapy

	Higher PEEP (*n* =)	Lower PEEP (*n* =)	Absolute Difference (95% CI)	*p* value
Fluids				
Total fluid intake, mL				
Hydroxyethyl starch – no. (%)				
Dose, mL				
Gelatin – no. (%)				
Dose, mL				
Crystalloids – no. (%)				
Dose, mL				
Albumin – no. (%)				
Dose, mL				
Vasopressors				
Dobutamine – no. (%)				
Dose, mg				
Ephedrine – no. (%)				
Dose, mg				
Adrenaline – no. (%)				
Dose, mg				
Noradrenaline – no. (%)				
Dose, mg				
Phenylephrine – no. (%)				
Dose, mg				
Blood products				
Packed red blood cells – no. (%)				
Dose, mL				
Fresh frozen plasma – no. (%)				
Dose, mL				
Platelets – no. (%)				
Dose, mL				

Data are median (quartile 25th - quartile 75th) or N / total (%).
Abbreviations: PEEP is positive end-expiratory pressure.

eTable 11 – Sensitivity Analyses for the Primary Outcome

	Higher PEEP (*n* = XXX)	**Lower PEEP (*n* = XXX)**	**Odds Ratio (95% CI)**	***p* value**
Count events*				
Median (quartile 25th – quartile 75th)				
Common effect GEE**				
Treatment-component interaction GEE***				
Average relative effect GEE****				

Abbreviations: CI is confidence interval; GEE is generalized estimating equations; PEEP is positive end expiratory pressure.

* 95% confidence intervals calculated with proportional odds logistic regression and *p* values calculated Wilcoxon rank-sum test

** 95% confidence intervals and *p* values calculated in a common effect GEE model (estimating a single treatment effect across all 10 components)

*** *p* value calculated in a GEE model (test whether the treatment effect differs across the 10 components)

**** *p* value calculated in a GEE model (estimating, then averaging, the 10 distinct treatment effects)

PROPOSED FIGURE 1