Statistical Analysis Plan of the 'Driving Pressure During General Anesthesia for Open Abdominal Surgery' trial (DESIGNATION)

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INTRODUCTION

The ‘Driving Pressure During General Anesthesia for Open Abdominal Surgery’ randomized clinical trial (DESIGNATION) compares an intraoperative ventilation strategy with individualized high positive end–expiratory pressure (PEEP) with recruitment maneuvers (‘individualized high PEEP’) to a conventional strategy with standard PEEP of 5 cmH_2O without recruitment maneuvers (‘low PEEP’).[1] The primary objective of this study is to determine whether ‘individualized high PEEP’ is superior to a ‘low PEEP’ with regard to the incidence of postoperative pulmonary complications (PPC). Enrollment of patients in DESIGNATION already started and the study is planned to finish around 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 DESIGNATION trial.

METHODS

Design, ethics and registration

DESIGNATION is an international, multicenter, parallel, two–group, prospective, randomized, patient and outcome–assessor blinded superiority clinical trial designed to determine if an individualized intra–operative high PEEP strategy guided by the driving pressure (ΔP) is superior to a standard low PEEP strategy with respect to the development of PPC in adult patients that are at risk for PPC and submitted to open abdominal surgery.

The protocol, with a detailed description of the study population, the two strategies and follow–up plan of the DESIGNATION trial was published elsewhere.[1] The DESIGNATION trial was approved by the Institutional Review Board of the Amsterdam University Medical Centers, location Academic Medical Center, in Amsterdam, The Netherlands (2018_319, February 7, 2019) and is registered with clinicaltrials.gov (NCT03884543).

Randomization and blinding

Eligible patients are randomly allocated in a 1:1 ratio to the 'individualized high PEEP' or 'low PEEP' strategy. The allocation sequence is computer–generated by an independent investigator using permuted blocks of different block sizes, with a maximum block size of eight and stratified per center and BMI (≤ 30 vs. > 30 kg/m^2). 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 investigator randomizes the patients immediately before surgery and is responsible for the trial intervention and data collection. A second investigator remains blinded for the randomization and is responsible for postoperative data

collection. The surgeon and patient are kept blind to the allocated ventilation strategy. Since PEEP can be adjusted at any time point upon the surgeons' request or because of concerns about patient's safety, and since patients do not profit from knowing to which group they are allocated to, unblinding is not applicable.

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 studies.[2-4] Patients who develop a least one complication are considered as meeting the primary outcome. The components of the composite outcome of PPC have been defined elsewhere,1 and these include: 1) severe respiratory failure; 2) bronchospasm; 3) suspected pulmonary infection; 4) new pulmonary infiltrates; 5) aspiration pneumonitis; 6) new atelectasis; 7) acute respiratory distress syndrome (ARDS); 8) new pleural effusion; 9) new cardiopulmonary edema; and 10) new pneumothorax. The selected PPC can sensibly be added together as they share common pathophysiological mechanisms and have plausibility to be affected in the same direction by the intervention to be tested in this study. If pulmonary infiltrates, pleural effusion, atelectasis, cardiopulmonary edema or pneumothorax are already present in any preoperative chest imaging and did not worsen, the patient will not be coded as a new complication in the postoperative period if present.

Secondary outcomes also have been defined elsewhere,[1] and include: 1) mild respiratory failure; 2) a composite outcome of intraoperative complications, including desaturation, hypotension, any need for vasoactive agents, and any

new arrhythmias; 3) postoperative extrapulmonary complications; 4) intraoperative fluid balance; 5) impaired wound healing; 6) unplanned admission to an ICU; 7) length of intensive care unit (ICU) stay (if applicable); 8) length of hospital stay; and 9) all–cause hospital mortality. 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 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 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 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

DESIGNATION is designed to enroll a total of 1.468 patients (734 in each arm). This number allows the detection of a reduction in the incidence of the primary outcome from 34% in the control group to 27.2% in the experimental group (relative risk reduction of 20%), considering a type I error of 5%, a power of 80%,

similar allocation ratio between the arms (1:1) and a dropout rate of 2%. The required sample size is calculated based on an estimated effect size derived from individual patient data from previous trials.[3-8]

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. Variables will be expressed as counts and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR) whenever appropriate.

The primary and 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.[9] 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.

Adherence to study interventions and ventilatory variables

Surgical and perioperative characteristics will be reported (**Tables 4** and **5**). 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 constructed (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 **Table 6**. 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 'individualized high PEEP' compared to low PEEP of 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 (**Table 7**). To support interpretation, a confidence distribution for the primary outcome using a normal approximation on the estimated absolute difference will be calculated.[10] The confidence distribution will be computed to provide the frequentist probability that the absolute difference is less than 0.[10] In addition, the confidence distribution will be reported in a plot.

Secondary outcomes

For binary outcomes, the effect of 'individualized high PEEP' compared to 'low 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. 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. In addition, a Holm–Bonferroni correction to control the family–wide error rate to the *p* values for all 17 secondary outcomes will be done and presented in a Table.

Per–protocol analysis

The analysis for the primary endpoint will be repeated in patients who received treatment according to their respective randomisation arm. This includes patients with pre-approved protocol deviations. However, patients with non-pre-approved protocol deviations and protocol violations will be excluded.

Subgroup analysis

Treatment effects on incidence of PPC will be analyzed according to the following predefined subgroups: 1) age < 65 years *vs* ≥ 65 years; 2) body mass index < 30 kg/m^2 *vs* BMI ≥ 30 kg/m^2; 3) baseline SpO_2 < 96% *vs* SpO_2 ≥ 96%; 4) moderate *vs* high risk for PPC according to the ARISCAT risk score (< 45 vs. ≥ 45); 5) duration of surgery < 3 hours *vs* ≥ 3 hours; and 6) planned destination to ICU or HDU *vs* ward. 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

Since the primary outcome of the present study is a composite one, the choice of the statistical method is an important part of designing because 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 proportional odds 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 99.5% Bonferroni–corrected confidence intervals will be reported (1 – 0.05/10 = 0.995);

- 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.

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Table 1 – Definitions of Outcomes

Outcomes	Definition
Severe respiratory failure	Need for noninvasive or invasive mechanical ventilation, or a PaO_2 < 60 mmHg (or < 7.9 kPa) or SpO_2 < 90% despite supplemental oxygen in spontaneously breathing patients.
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators.
Suspected pulmonary infection	Receiving antibiotics and meeting at least one of the following criteria: • New or changed sputum; • New or changed lung opacities on chest radiograph when clinically indicated; • Tympanic temperature > 38.3 °C; • White blood cell count > 12,000/μL.
Pulmonary infiltrates	Any unilateral or bilateral infiltrates on chest radiography.
Aspiration pneumonitis	Respiratory failure after the inhalation of regurgitated gastric contents.
Atelectasis	Lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectasis lung on chest radiography.
Acute respiratory distress syndrome	According to the Berlin criteria for acute respiratory distress syndrome*.
Pleural effusion	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 on chest radiography.
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.
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiography.
Mild respiratory failure	PaO_2 < 60mmHg (or < 7.9 kPa) or SpO_2 < 90% in room air, but responding to supplemental oxygen (excluding hypoventilation).
Intraoperative desaturation	SpO_2 ≤ 90% or if preoperative SpO_2 < 90% an absolute decrease in SpO_2 > 5% and lasting > 1 minute.
Intraoperative hypotension	Decrease in mean arterial pressure of > 20% and lasting for > 3 minutes.
Intraoperative need for vasoactive agents	Vasoactive agents more than needed to compensate for vasodilating effects of anesthesia.
Intraoperative arrhythmias	Needing intervention as suggested by the Advanced Cardiac Life Support Guidelines**.
Sepsis	According to SEPSIS-3 criteria***.
Septic shock	According to SEPSIS-3 criteria***.
Extrapulmonary infection	Wound infection plus any other infection.
Acute kidney injury	According to Acute Kidney Injury Network (AKIN) criteria****

* ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
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Table 2 – 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 Intraoperative Characteristics *A table showing additional intraoperative characteristics.*
eTable 3	Rescue Therapies in Included Patients *A table showing the steps of rescue therapies in patients receiving rescue in each arm.*
eTable 4	Protocol Deviations *A table reporting the protocol deviations in each arm.*
eTable 5	Daily Assessment of Included Patients *A table showing characteristics over the first 5 days of follow-up.*
eTable 6	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 7	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	Characteristics of the Intervention *A, Line plot reporting the mean and 95% confidence interval of the driving pressure after intubation, after recruitment maneuver, during first and second hour of surgery and at the last hour by treatment group.* *B, Bar plot reporting the mean difference in driving pressure between groups after intubation, after recruitment maneuver, during first and second hour of surgery and at the last hour.* *C, Bar plot showing the titrated level of PEEP in the individualized high PEEP group.* *D, Line plot showing the plateau pressure and driving pressure according to PEEP levels during the PEEP titration maneuver in the individualized high PEEP.*
eFigure 2	Level of PEEP in the Study Population *Histogram reporting the most used level of PEEP during the first five hours of the surgical procedure by treatment group.*
eFigure 3	Tidal Volume, PEEP, Peak Pressure, Plateau Pressure, FiO_2 and SpO_2 During Surgery *Line graph reporting the mean and 95% confidence interval of the variables after intubation, after recruitment maneuver, during first and second hour of surgery and at the last hour by treatment group.*
eFigure 4	VAS 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 5	Patient Status in the First Five Days of Follow-Up

	Transition plot showing the status of the patients in the first five days of follow-up.
eFigure 6	Confidence Distribution for the Primary Outcome *Confidence distribution of the estimated absolute difference of the primary outcome of Individualized High PEEP versus Low PEEP constructed using a normal approximation. A, The full confidence distribution of the estimated absolute difference, with the dashed vertical line indicating the median value and the area highlighted in tan indicating the 95% confidence interval. The orange area is related to an absolute difference greater than 0 (i.e., the intervention is associated with higher incidence of PPC vs standard care). The dotted line at an absolute difference of 0 indicates no treatment effect. The figure demonstrates that the confidence probability that Individualized High PEEP is associated with a reduced incidence of PPC (to any extent) compared with Low PEEP is XX.X%.* *B, The cumulative confidence distribution of the estimated absolute difference, with the y-axis corresponding to the confidence the absolute difference is less than or equal to the value on the x-axis. The blue-gray area indicates a beneficial intervention (i.e., absolute difference lower than 0). The dashed vertical line indicates the median.*
eFigure 7	Results of the Sensitivity Analyses for the Primary Outcome *Forest plot reporting the results of all sensitivity analyses*

Table 3 (Table 1) – Baseline Characteristics of the Included Patients

	Individualized High PEEP (*n* = XXX)	**Low PEEP (*n* = XXX)**
Age, years		
Age ≥ 65 years – no. (%)		
Male gender – no. (%)		
Weight, kilograms		
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		
Functional status – no. (%)		
Independent		
Partially dependent		
Totally dependent		
Co-existing disorders – no. (%)		
Diabetes		
Coronary artery disease		
COPD		
Smoker		
Never		
Former*		
Current		
Active cancer		
Type of surgery – no. (%)		
Urgent		
Elective		
Procedure – no. (%)**		
Gynecology		
Urology		
Vascular		
Pancreatic		
Bowel		
Liver		
Gastric		
Hepatic		
Biliary		
Other		
Preoperative vital signs		
Heart rate, bpm		

Table 3 (Table 1) – Baseline Characteristics of the Included Patients

	Individualized High PEEP (*n* = XXX)	**Low PEEP (*n* = XXX)**
Systolic blood pressure, mmHg		
Mean arterial pressure, mmHg		
Respiratory rate, breaths/min		
Temperature, ºC		
SpO_2, %		
SpO_2 < 96% - no. (%)		
Preoperative chest X-ray – no. (%)		
Infiltrates		
Pleural effusion		
Atelectasis		
Preoperative laboratory		
Hemoglobin, g/dL		
Creatinine, mg/dL		

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; COPD is chronic obstructive pulmonary disease; SpO_2 is pulse oximetry.

* Cessation more than 3 months.

** A patient can have more than one.

Table 4 (Table 2) – Ventilation and Intraoperative Characteristics

	Individualized High PEEP (*n* = XXX)	Low PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Recruitment maneuver – no. (%)				
Number of recruitment maneuvers				
Lowest ΔP during PEEP titration, cmH2O				
Tidal volume, mL/kg PBW				
After intubation				
During first hour				
Last hour				
PEEP, cmH_2O				
After intubation				
During first hour				
Last hour				
Peak pressure, cmH_2O				
After intubation				
During first hour				
Last hour				
Plateau pressure, cmH_2O				
After intubation				
During first hour				
Last hour				
Driving pressure, cmH_2O				
After intubation				
During first hour				
Last hour				
Respiratory rate, breaths/min				
After intubation				
During first hour				
Last hour				
FiO_2				
After intubation				
During first hour				
Last hour				
SpO_2, %				
After intubation				
During first hour				
Last hour				
$etCO_2$, mmHg				
After intubation				
During first hour				
Last hour				

Table 4 (Table 2) – Ventilation and Intraoperative Characteristics

	Individualized High PEEP (*n* = XXX)	Low PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Mean arterial pressure, mmHg				
After intubation				
During first hour				
Last hour				
Duration of anesthesia, min				
Duration of surgery, min				
Duration of surgery ≥ 180 min – no. (%)				
Maintenance of anesthesia – no. (%)				
Volatile				
Totally intravenous anesthesia				
Combine				
Epidural – no. (%)				
Thoracic				
Lumbar				
Neuromuscular monitoring – no. (%)				
Residual paralysis at extubation– no. (%)				
Paralysis reverted – no. (%)				
Temperature at the end of the surgery, ºC				
Fluids				
Total intake, mL				
Crystalloids intake, mL				
Colloid – no. (%)				
Colloid intake, mL				
Total output, mL				
Urine output, mL				
Blood loss, mL				
Fluid balance, mL				
Transfusion – no. (%)				
Packed red blood cells				
Fresh frozen plasma				
Platelets				
Unplanned ICU/HDU admission – no. (%)				

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

Abbreviation: ΔP is driving pressure, 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, ICU is intensive care unit, HDU is high dependency unit.

Table 5 (eTable 2) – Additional Intraoperative Characteristics

	Individualized High PEEP (*n* = XXX)	Low PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Fluids				
Total intake, mL				
Crystalloids – no. (%)				
Cumulative intake, mL				
Colloid – no. (%)				
Cumulative intake, mL				
Total output, mL				
Urine output – no. (%)				
Cumulative output, mL				
Blood loss – no. (%)				
Cumulative loses, mL				
Fluid balance, mL				
Vasopressors				
Dobutamine – no. (%)				
Cumulative dose, mg				
Dopamine – no. (%)				
Adrenaline – no. (%)				
Cumulative dose, mg				
Ephedrine – no. (%)				
Cumulative dose, mg				
Noradrenaline – no. (%)				
Cumulative dose, mg				
Phenylephrine – no. (%)				
Cumulative dose, mg				
Transfusion				
Packed red blood cells – no. (%)				
Cumulative amount, mL				
Fresh frozen plasma – no. (%)				
Cumulative amount, mL				
Platelets – no. (%)				
Cumulative amount, mL				

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

Table 6 (eTable 3) – Daily Assessment of Included Patients

	Individualized High PEEP (*n* = XXX)	Low PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Day 1				
Patients in hospital – no. (%)				
Admission to ICU – no. (%)				
Mechanical ventilation – no. (%)				
Invasive				
Non-invasive				
Physiotherapy – no. (%)				
Renal replacement therapy – no. (%)				
VAS pain				
Respiratory rate, breaths/min				
SpO_2, %				
Mean arterial pressure, mmHg				
Day 2				
Patients in hospital – no. (%)				
Admission to ICU – no. (%)				
Mechanical ventilation – no. (%)				
Invasive				
Non-invasive				
Physiotherapy – no. (%)				
Renal replacement therapy – no. (%)				
VAS pain				
Respiratory rate, breaths/min				
SpO_2, %				
Mean arterial pressure, mmHg				
Day 3				
Patients in hospital – no. (%)				
Admission to ICU – no. (%)				
Mechanical ventilation – no. (%)				
Invasive				
Non-invasive				
Physiotherapy – no. (%)				
Renal replacement therapy – no. (%)				
VAS pain				
Respiratory rate, breaths/min				
SpO_2, %				
Mean arterial pressure, mmHg				
Day 4				
Patients in hospital – no. (%)				
Admission to ICU – no. (%)				
Mechanical ventilation – no. (%)				
Invasive				

Table 6 (eTable 3) – Daily Assessment of Included Patients

	Individualized High PEEP (*n* = XXX)	Low PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Non-invasive				
Physiotherapy – no. (%)				
Renal replacement therapy – no. (%)				
VAS pain				
Respiratory rate, breaths/min				
SpO_2, %				
Mean arterial pressure, mmHg				
Day 5				
Patients in hospital – no. (%)				
Admission to ICU – no. (%)				
Mechanical ventilation – no. (%)				
Invasive				
Non-invasive				
Physiotherapy – no. (%)				
Renal replacement therapy – no. (%)				
VAS pain				
Respiratory rate, breaths/min				
SpO_2, %				
Mean arterial pressure, mmHg				

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

Abbreviations: PEEP is positive end-expiratory pressure, ICU is intensive care unit, VAS is visual analogue scale, SpO_2 is pulse oximetry.

Table 7 (Table 3) – Primary and Secondary outcomes

	Individualized High PEEP (*n* = XXX)	Low PEEP (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Primary outcome				
Postoperative pulmonary complications – no. (%)				
Severe respiratory failure				
Bronchospasm				
Suspected pulmonary infection				
Pulmonary infiltrates				
Aspiration pneumonitis				
Atelectasis				
Acute respiratory distress syndrome				
Pleural effusion				
Cardiopulmonary edema				
Pneumothorax				
Secondary outcomes				
Mild respiratory failure – no. (%)				
Intraoperative complications – no. (%)				
Desaturation				
Hypotension				
Need for vasoactive agents				
New arrhythmias				
Postoperative extrapulmonary complications – no. (%)				
Sepsis				
Septic shock				
Extrapulmonary infection				

Anastomotic leakage	
Acute kidney injury	
Intraoperative fluid balance – no. (%)	
Impaired wound healing – no. (%)	
Unplanned admission to intensive care unit – no. (%)	
Intensive care unit length of stay, days	
Hospital length of stay, days	
All-cause hospital mortality – no. (%)	

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

MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN (*TRIALS* 2020; 21:198)	UPDATE IN THE SAP (Closed in January 12, 2024)	INCLUDED IN THE NEW SAP (Updated in January 12, 2025)
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 ICU and hospital length of stay	Generalized linear models considering distributions that will fit a possible heavy right-tailed distribution without zero (such as truncated Poisson, gamma distribution, or inverse Gaussian), choosing the best fit according to the model's deviance.	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	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.	---
Subgroup analysis	Analyses of heterogeneity of effects across subgroups will be performed with the use of treatment-by-subgroup interaction term, added to a generalized linear model considering a binomial distribution, and will be 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.	---
Additional analyses	Not described.	Since the primary outcome of the present study is a composite one, the choice of the statistical method is an important part of designing because various methods	---

		provide different power, depending on the situation. In addition to the standard analysis described above, additional analyses will be performed.	
Confidence distribution	Not described.	Not described.	To support interpretation, a confidence distribution for the primary outcome using a normal approximation on the estimated absolute difference will be calculated. The confidence distribution will be computed to provide the frequentist probability that the absolute difference is less than 0.10 In addition, the confidence distribution will be reported in a plot.

Abbreviations: ICU: intensive care unit.

PROPOSED FIGURE 1