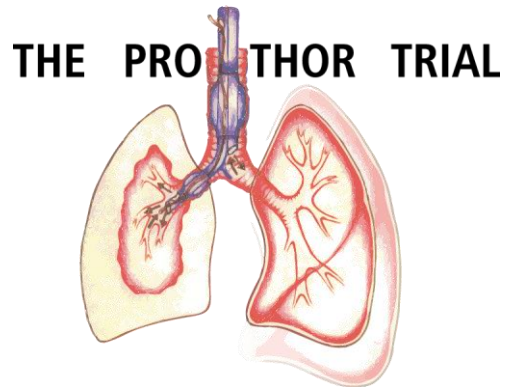


RESEARCH PROTOCOL



**PROtective ventilation with high versus low PEEP
during one-lung ventilation for THORacic surgery –
PROTHOR: A randomized controlled trial**

Ver 2.3

For the PROVE NETWORK Investigators

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The information given in this study protocol is to be treated as strictly confidential. It only serves to inform the investigators and other persons involved in the conduct of the study as well as the Ethics Committee and the Authorities.

This study protocol may not be given to noninvolved persons without the permission of the Principal Investigator, Mert Sentürk.

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1 LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
ALI	Acute Lung Injury
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CA	Competent Authority
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
EU	European Union
ICU	Intensive Care Unit
NPPV	Noninvasive Positive Pressure Ventilation
OLV	One-Lung Ventilation
OSA	Obstructive Sleep Apnea
PBW	Predicted Body Weight
PEEP	Positive end–expiratory pressure
PPC	Postoperative Pulmonary Complication
ppo	Predictive postoperative
RM	Recruitment Maneuver
VILI	Ventilator–induced lung injury

2 SUMMARY

SUMMARY

Rationale	One-lung ventilation (OLV) with resting of the contralateral lung may be required to allow or facilitate thoracic surgery. However, OLV can result in severe hypoxemia, requiring a mechanical ventilation approach that is able to maintain adequate gas exchange, while protecting the lungs against postoperative pulmonary complications (PPCs). During OLV, the use of lower tidal volumes (V_T) is helpful to avoid over-distension, but can result in increased atelectasis and repetitive collapse-and-reopening of lung units, particularly at low levels of positive end-expiratory pressure (PEEP). Nevertheless, it is not known if, during OLV with low V_T , high levels of PEEP combined with lung recruitment maneuvers are superior to low to moderate PEEP for protection against PPCs.
Objectives	To compare a strategy using high PEEP (10 cmH ₂ O) with recruitment maneuvers versus low PEEP (5 cmH ₂ O) without recruitment maneuvers, during thoracic surgery under standardized OLV with low V_T (5 mL/kg predicted body weight – PBW) in adults.
Hypothesis	We hypothesize that in adult patients undergoing thoracic surgery under standardized OLV with low V_T , high PEEP and recruitment maneuvers as compared to low PEEP without recruitment maneuvers prevent PPCs.
Study design	An international multicenter randomized controlled trial.
Study population	Adult patients with body mass index (BMI) < 35 kg/m ² undergoing thoracic surgery with OLV.
Primary endpoint	<ul style="list-style-type: none">• The proportion of patients developing one or more PPCs
Secondary endpoints	<ul style="list-style-type: none">• intraoperative complications• postoperative extra-pulmonary complications• extended PPCs• need for unexpected ICU admission or ICU readmission• number of hospital-free days at day 28• 90-day survival• arterial blood gas analysis during OLV, TLV (pCO₂, pO₂, pH)• any postoperative respiratory intervention (e.g. NIV or CPAP or intubation or High Flow Nasal Cannula)

Inclusion criteria	<ul style="list-style-type: none"> • Patient scheduled for open thoracic or video-assisted thoracoscopic surgery under general anesthesia requiring OLV (no emergency surgery) • BMI < 35 kg/m² • age ≥ 18 years • expected duration of surgery > 60 min • planned lung separation with double lumen tube (DLT, not for study purpose only) • most of ventilation time during surgery expected to be in OLV
Exclusion criteria	<ul style="list-style-type: none"> • COPD GOLD grades III and IV, lung fibrosis, documented bullae, severe emphysema, pneumothorax • uncontrolled asthma • Heart failure NYHA Grade 3 and 4, Coronary Heart Disease CCS Grade 3 and 4 • previous lung surgery • documented pulmonary arterial hypertension >25mmHg MPAP at rest or > 40 mmHg syst. (estimated by ultrasound) • documented or suspected neuromuscular disease (thymoma, myasthenia, myopathies, muscular dystrophies, others) • planned mechanical ventilation after surgery • bilateral procedures • lung separation with other method than DLT (e.g. difficult airway, tracheostomy) • surgery in prone position • persistent hemodynamic instability, intractable shock • intracranial injury or tumor • enrollment in other interventional study or refusal of informed consent • pregnancy (excluded by anamnesis and/or laboratory analysis) • esophagectomy, pleural surgery only, sympathectomy surgery only, chest wall surgery only, mediastinal surgery only, lung transplantation • presence before induction of anaesthesia of one of the adverse events, listed as postoperative pulmonary complications (aspiration, moderate respiratory failure, infiltrates, pulmonary infection, atelectasis, cardiopulmonary edema, pleural effusion,

	<p>pneumothorax, pulmonary embolism, purulent pleuritis, lung hemorrhage)</p> <ul style="list-style-type: none"> • documented preoperative hypercapnia > 45mmHg (6kPa)
Randomization Procedure	Randomization will be performed using a dedicated website and stratified per center. Central randomization with the use of a permuted-block randomization list (block lengths of 4, 6 or 8, random sequence) will be used.
Consent & Insurance	All patients must provide written informed consent according to local regulations before inclusion in the study. Patient insurance has to be granted according to local regulations.
Sample size	<p>For this trial we have planned the group sequential methods design, which gives us the possibility for early stopping of the study if the intervention shows a statistically significant advantage at an interim look, but also allows early stopping for futility if the interim analysis reveals that, with high probability, the trial will end up negative.</p> <p>Sample size calculation was based on our primary study endpoint, taking data collected from a subset of patients undergoing OLV for thoracic surgery in a prospective observational, multicenter, international study (LAS VEGAS) into account. LAS VEGAS showed an incidence of approximately 23% for a PPC composite comparable to the present definition. Assuming a significance level of 0.05 and a power of 90%, to detect the expected difference in postoperative pulmonary complications between the high PEEP group of 17,25% and the low PEEP group of 23% (risk ratio of 0.75), a sample size of 2259 has been calculated. Assuming a dropout rate of 5% a total of 2378 patients have to be included in the study.</p>
Study groups	<p>Patients will be randomly assigned to one of two groups:</p> <p>LOW PEEP GROUP: mechanical ventilation with V_T of 5 mL/kg (PBW) during OLV and PEEP of 5 cmH₂O without recruitment maneuvers</p> <p>HIGH PEEP GROUP: mechanical ventilation with V_T of 5 mL/kg (PBW) during OLV and PEEP of 10 cmH₂O and recruitment maneuvers</p>
Postoperative pulmonary complications (details see Appendix)	<ul style="list-style-type: none"> • aspiration pneumonitis • moderate respiratory failure • severe respiratory failure • pulmonary embolism • ARDS (according to the Berlin Definition)

	<ul style="list-style-type: none"> • pulmonary infiltrates (non-surgery lung) • pulmonary infection • atelectasis • cardiopulmonary edema • pleural effusion • pneumothorax (on non-surgery lung) • prolonged air leakage • purulent pleuritis • lung hemorrhage • extended PPCs: bronchospasm, mild respiratory failure
Lung separation	Lung separation has to be performed by DLT technique. Confirmation of adequate placement of the lung separation device using fiberoptic bronchoscopy or a similar technique for visualization (for example, tubes with embedded cameras) is mandatory.
Mechanical ventilation	<p>Mechanical ventilation will be applied in volume–controlled mode.</p> <p>During two-lung ventilation (TLV), V_T will be set at 7 mL/kg PBW. Further settings will be $FIO_2 \geq 0.4$, inspiratory to expiratory ratio (I:E) range of 1:1 to 1:2, and respiratory rate adjusted to normocapnia ($PaCO_2$ between 35 and 45 mmHg).</p> <p>During OLV, V_T will be decreased to 5 mL/kg PBW, while keeping other settings initially unchanged. If peak pressure > 40 cm H₂O, or plateau pressure > 30 cmH₂O occurs, first the I:E ratio will be changed (range 1:1 - 1:2). Thereafter, V_T will be decreased in steps down to 4.0 mL/kg. If auto-PEEP is suspected, change of respiratory rate or I:E ratio according to the judgement of the treating physician is allowed.</p>
Respiratory management (see below for details)	<ol style="list-style-type: none"> 1. Recruitment maneuver <ul style="list-style-type: none"> • Recruitment maneuver of the ventilated lung(s) – HIGH PEEP GROUP • Recruitment maneuver of the non-ventilated lung – BOTH GROUPS 2. Hypoxemia Rescue therapy <ul style="list-style-type: none"> • Hypoxemia Rescue – HIGH PEEP GROUP - before and after OLV • Hypoxemia Rescue - LOW PEEP GROUP - before and after OLV • Hypoxemia Rescue - HIGH PEEP GROUP - during OLV <p>Hypoxemia Rescue – LOW PEEP GROUP - during OLV</p> 3. Hypercapnia Rescue therapy <ul style="list-style-type: none"> • Hypercapnia Rescue – BOTH GROUPS - during OLV

INTRODUCTION AND RATIONALE

2.1 Postoperative pulmonary complications

Postoperative pulmonary complications (PPCs), especially postoperative respiratory failure, add to the morbidity and mortality of surgical patients [1, 2]. An ARISCAT score ≥ 26 is associated with an intermediate-to-high risk of PPCs [3].

2.2 Ventilator-associated lung injury

Even though mechanical ventilation is a life-saving strategy in patients with respiratory failure and frequently necessary during general anesthesia, both experimental[3-5] and clinical[6-8] studies show that mechanical ventilation has the potential to aggravate or even initiate lung injury (so-called ventilator-induced lung injury, VILI). Repetitive collapse/reopening of lung units (atelectrauma) and overdistension of lung units (volutrauma) are possible mechanisms underlying VILI [9-11]. While positive end-expiratory pressure (PEEP) can minimize atelectrauma, lower tidal volumes are thought to reduce volutrauma. One meta-analysis showed that use of lower tidal volumes is associated with a better outcome for patients with uninjured lungs[12]. This study included both surgery patients who underwent mechanical ventilation for general anesthesia as well as critically ill patients who required longer mechanical ventilation. Notably, a more recent meta-analysis showed a decrease in lung injury development, pulmonary infection and atelectasis in patients receiving intraoperative mechanical ventilation with both lower tidal volumes and higher levels of PEEP [13].

2.3 Postoperative pulmonary complications and mechanical ventilation

Mechanical ventilation is frequently required in patients undergoing surgery. Our group has shown that an intraoperative ventilation strategy with lower V_T and PEEP may improve postoperative lung function [14] and even outcome [13] in patients undergoing open abdominal surgery. In contrast, when low V_T is used, the use of high PEEP combined with recruitment maneuvers, as compared to low PEEP without recruitment maneuvers, does not add to the protection against PPCs in those patients [15].

2.4 Mechanical ventilation and ventilator induced lung injury in thoracic anesthesia

Different experimental and clinical studies have shown that inappropriate settings of OLV can promote VILI [16-18]. During OLV for thoracic surgery, the risk of VILI is even higher than in other types of surgery due to several factors, namely:

1. Lungs are submitted to surgical manipulation, with increased release of inflammatory mediators [19] added to the stress of mechanical ventilation

2. In lateral decubitus position, which is frequently used, the pressure on the dependent lung increases so that the risk of atelectasis formation is higher than usual [19]
3. Conventional methods to prevent and treat the hypoxemia during OLV can be harmful to the lung tissue: high FIO_2 and low (or no) PEEP both can promote atelectasis, whereas high V_T can cause baro- and volutrauma [20]

Therefore, it is not known whether during OLV with low V_T for thoracic surgery, a strategy using high PEEP combined with recruitment maneuvers protects against PPCs, as compared to low PEEP without recruitment maneuvers.

3 OBJECTIVES AND HYPOTHESIS

3.1 Objectives

To compare a strategy using high PEEP (10 cmH₂O) with recruitment maneuvers versus low PEEP (5 cmH₂O) without recruitment maneuvers, during thoracic surgery under standardized OLV with low V_T in adults.

3.2 Hypothesis

We hypothesize that in adult patients undergoing thoracic surgery under standardized OLV with low V_T, high PEEP and recruitment maneuvers as compared to low PEEP without recruitment maneuvers prevent PPCs.

4 STUDY DESIGN

An international multicenter randomized controlled trial.

5 STUDY POPULATION

5.1 Inclusion criteria

- Patient scheduled for open thoracic or video-assisted thoracoscopic surgery under general anesthesia requiring OLV (no emergency surgery)
- BMI < 35 kg/m²
- age ≥ 18 years
- expected duration of surgery > 60 min
- planned lung separation with double lumen tube (DLT, not for study purpose only)
- most of ventilation time during surgery expected to be in OLV

5.2 Exclusion criteria

- COPD GOLD Grade III and IV, lung fibrosis, documented bullae, severe emphysema, pneumothorax
- uncontrolled asthma
- Heart failure NYHA Grade 3 and 4, Coronary Heart Disease CCS Grade 3 and 4
- previous lung surgery
- documented pulmonary arterial hypertension >25mmHg MPAP at rest or > 40 mmHg syst. (estimated by ultrasound)
- documented or suspected neuromuscular disease (thymoma, myasthenia, myopathies, muscular dystrophies, others)
- planned mechanical ventilation after surgery
- bilateral procedures
- lung separation with other method than DLT (e.g. difficult airway, tracheostomy)
- surgery in prone position
- persistent hemodynamic instability, intractable shock
- intracranial injury or tumor
- enrollment in other interventional study or refusal of informed consent
- pregnancy (excluded by anamnesis and/or laboratory analysis)
- esophagectomy, pleural surgery only, sympathectomy surgery only, chest wall surgery only, mediastinal surgery only, lung transplantation
- presence of one of the adverse events, listed as postoperative pulmonary complication (aspiration, moderate respiratory failure, infiltrates, pulmonary infection, atelectasis, cardiopulmonary edema, pleural effusion, pneumothorax, pulmonary embolism, purulent pleuritis, lung hemorrhage)
- documented preoperative hypercapnia > 45mmHg (6kPa)

5.3 Sample size calculation

For this trial we have planned to use an adaptive trial design, 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 gives us the possibility for early stopping of the study if the experimental treatment shows a statistically significant therapeutic advantage at an interim look, but also allows early stopping for futility if the interim analysis reveals that, with high probability, the trial will end up negative.

Sample size calculation was based on our primary study endpoint, taking data collected from a subset of patients undergoing OLV for thoracic surgery in a prospective observational, multicenter, international study (LAS VEGAS) into account. LAS VEGAS showed an incidence of approximately 23% for a PPC composite comparable to the present definition. Assuming a significance level of 0.05 and a power of 90%, to detect the expected difference in postoperative pulmonary complications between the high PEEP group of 17,25% and the low PEEP group of 23% (risk ratio of 0.75), a sample size of 2259 has been calculated. Assuming a dropout rate of 5% **a total of 2378 patients** have to be included in the study.

We used the software package East[®] for sample size calculations (East[®], Version 6.3.1., Cytel Inc, USA) The Difference of Proportions test has been used to compare the independent samples from two populations (Group Sequential Design for a Binomial Superiority Trial; discrete endpoint two sample test; parallel design; difference of proportions; using the unpooled estimate of variance). The sample size calculation was done with the following parameters: Superiority Design, 2-sided test; alpha 0,05; Power 0,9, allocation ratio 1; Proportion₁=0,23; Proportion₂=0,1725; Difference in Proportions=-0,058.

We used an alpha-spending function 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 we have a moderate hurdle for early stopping for efficacy and a reasonable chance to stop early if the trial is going nowhere.

We constructed a non-binding futility boundary 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.

We planned to take 5 interim looks at the data for evidence of efficacy, harm, and/or futility with the aim of possibly stopping the trial early. The planned number of looks 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 looks will be equal. Therefore, interim analyses will be performed after 20% (476 patients), 40% (952 patients), 60% (1426 patients), 80% (1902 patients) and 100% of patients (2378 in total) included.

Patients will be randomly assigned to one of the two groups using a website based data entry and randomization platform (RedCAP, Ver 6.6.2 Vanderbilt University, Tennessee, USA). Randomization will be conducted using blocks of 4, 6 and 8 patients, in alleatory fashion. Thereby, group sizes will be comparable at interim analyses, which will be conducted in a group-blinded manner.

5.4 Anticipated duration

We estimate that 50 centers will participate in this trial, and that one year will be necessary for all centers to start including patients. If each center includes one patient per week, patient inclusion shall last one year. Based on our experience with large randomized controlled trials, data clearing and analysis, and compilation of the manuscript will require a further year; totalling 3 years for the entire project.

6 METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

- Postoperative pulmonary complications

6.1.2 Secondary study parameters/endpoints

- Intra-operative complications, i.e., complications related to the ventilation strategy (for example: hypoxemia, defined as SpO₂ < 90% for > 1 min; hypotension, as defined by systolic arterial pressure < 90 mmHg for > 2 min)
- postoperative extra-pulmonary complications
- extended PPCs
- need for unexpected ICU admission or ICU readmission
- number of hospital-free days at day 28
- 90-day survival
- arterial blood gas analysis during OLV, TLV (pCO₂, pO₂, pH)
- any postoperative respiratory intervention (e.g. NIV or CPAP or intubation or High Flow Nasal Cannula)

6.2 Patient Consent

All patients must provide written informed consent according to local regulations before inclusion in the study. A patient insurance has to be provided by each participating site, according to and depending on local rules.

6.3 Randomization

Randomization will be performed using a dedicated website and will be stratified per center. Central randomization with the use of a permuted-block randomization list (block lengths of 4, 6 or 8, random sequence) will be used. Before surgery, patients will be randomly assigned 1:1 to mechanical ventilation with PEEP of 5 cmH₂O without recruitment maneuvers (“low PEEP”) or mechanical ventilation with PEEP of 10 cmH₂O and recruitment maneuvers (“high PEEP”).

If hypoxemia, defined as SpO₂ < 90% for > 1 min, or hypercapnia (PETCO₂ > 60 mmHg) with respiratory acidosis (pHa < 7.20) occurs, rescue is performed according to the sub-section “rescue therapies for impaired gas exchange”.

At each site at least two investigators will be involved. The first investigator will be aware of the intervention and collect intra-operative data (Investigator 1). The second investigator will remain blinded to group assignment and assess outcome (Investigator 2).

6.4 Respiratory management

6.4.1 Lung separation

Adequate placement of the DLT must be confirmed by fiberoptic bronchoscopy or a similar technique of visualization (for example, DLT with embedded camera). Assessment of the DLT position only by auscultation of the chest is not acceptable.

6.4.2 Mechanical ventilation

Mechanical ventilation will be applied in volume–controlled mode. Following intubation and under TLV, the PEEP level will be set according to the randomization group, i.e. 5 cmH₂O in the low PEEP level group, and 10 cmH₂O in the high PEEP level group. In both groups, the PEEP will be maintained unchanged until extubation, unless rescue for hypoxemia requires adjustments (see “rescue therapies due to impaired gas exchange”). If auto-PEEP is suspected the respiratory rate or I:E ratio may be changed at discretion of the treating physician. Any deviation from the protocol has to be recorded.

In the high PEEP group, recruitment maneuvers will be performed:

- after bronchoscopy or disconnection of the ventilated lung from the mechanical ventilator
- after begin of OLV
- every one hour during OLV
- at the end of OLV after switching from OLV to TLV
- at end of surgery in supine position

During TLV, V_T will be set at 7 mL/kg predicted body weight (PBW). The PBW is calculated according to a predefined formula: $50 + 0.91 \times (\text{centimeters of height} - 152.4)$ for males and $45.5 + 0.91 \times (\text{centimeters of height} - 152.4)$ for females.

Further settings will be $FIO_2 \geq 0.4$, inspiratory to expiratory ratio (I:E) Range from 1:1 to 1:2, and respiratory rate adjusted to normocapnia ($PaCO_2$ between 35 and 45 mmHg).

During OLV, V_T will be decreased to 5 mL/kg PBW, while keeping other settings initially unchanged. If peak pressure > 40 cm H₂O, or plateau pressure > 30 cmH₂O occurs, first the I:E ratio will be changed to 1:1. Thereafter, V_T will be decreased down to 4.0 mL/kg PBW.

TWO-LUNG VENTILATION

Mode	Volume-controlled ventilation
Inspiratory V_T	7 mL/kg PBW
FiO_2	$\geq 40\%$, adjust to maintain $SpO_2 \geq 90\%$
I:E ratio	Range from 1:1 to 1:2
RR	adjusted to normocapnia ($PETCO_2 = 35-45\text{mmHg}$ or $4.6-6\text{kPa}$)
PEEP	if intrinsic-PEEP is suspected, change of respiratory rate or I:E ratio is allowed at discretion of the treating physician

ONE LUNG VENTILATION

Mode	Volume-controlled ventilation
Inspiratory V_T	5 mL/kg PBW (decrease to 4 mL/kg if $P_{\text{peak}} > 40$ cm H ₂ O, or $P_{\text{plat}} > 30$ cmH ₂ O)
FiO_2	$\geq 40\%$, adjust to maintain $SpO_2 \geq 90\%$
I:E ratio	Range from 1:1 to 1:2 (change to 1:1 if $P_{\text{peak}} > 40$ cm H ₂ O, or $P_{\text{plat}} > 30$ cmH ₂ O)
RR	adjusted to normocapnia ($PETCO_2 = 35-45\text{mmHg}$ or $4.6-6\text{kPa}$)
PEEP	if intrinsic-PEEP is suspected, change of respiratory rate or I:E ratio is allowed at discretion of the treating physician

6.4.3 Recruitment maneuver

Recruitment maneuver of the ventilated lung(s) – HIGH PEEP GROUP

The recruitment maneuver of the ventilated lung(s), will be performed in a hemodynamically stable patient (as judged by the anesthesiologist):

- after bronchoscopy
- at beginning of OLV
- every one hour during OLV
- at the end of OLV after switching from OLV to TLV
- at end of surgery in supine position
- following each disconnection from the mechanical ventilator

Recruitment maneuvers will be performed with stepwise increase of V_T in volume-controlled ventilation, as follows:

Recruitment maneuver of the ventilated lung(s) in the HIGH PEEP GROUP	<ol style="list-style-type: none"> 1. Increase FIO_2 to 1.0 2. Set peak inspiratory pressure limit to 45 cmH₂O 3. Set respiratory rate to 6 breaths/min 4. Set inspiratory to expiratory ratio (I:E) to 1:1 5. Increase V_T in steps of approximately 2 mL/kg PBW until plateau pressure reaches 30 to 40 cmH₂O 6. If the maximum V_T allowed by the anesthesia ventilator is achieved and the plateau pressure is lower than 30 cmH₂O, increase the PEEP as needed, but maximum 20 cmH₂O 7. Allow three breaths while maintaining plateau pressure of 30 to 40 cmH₂O 8. Set V_T, PEEP, respiratory rate, and I:E back to pre-recruitment values
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Recruitment maneuver of the non-ventilated lung – BOTH GROUPS

A recruitment maneuver of the non-ventilated lung may be necessary in both groups due to different reasons:

- a) detection of air leaks by request of surgeons
- b) as part of a rescue strategy due to hypoxemia
- c) before switching from OLV to TLV to re-expand the collapsed lung

Such maneuver should be performed in a hemodynamically stable patient (as judged by the anesthesiologist), and in agreement with the surgeon. To obtain standardization among centers, stepwise recruitment maneuvers of non-ventilated lungs will be performed with continuous positive airway pressure (CPAP), as follows:

Recruitment maneuver of the non-ventilated lung – BOTH GROUPS	<ol style="list-style-type: none"> 1. Keep the non-ventilated under visual inspection 2. Connect the CPAP device with adequate oxygen flow (FIO_2 1.0) to the non-ventilated lung 3. Set CPAP to 10 cmH₂O during 20 seconds 4. Set CPAP to 15 cmH₂O during 20 seconds 5. Set CPAP to 20 cmH₂O during 20 seconds <p>If performed as part of a rescue therapy, reduce CPAP to 10 cmH₂O and then 5 cmH₂O, otherwise disconnect the CPAP device</p>
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6.4.4 Hypoxemia rescue therapy

If hypoxemia, defined as **SpO₂ < 90%** for **> 1 min**, occurs, rescue should be performed.

<p>Hypoxemia Rescue – HIGH PEEP GROUP - before and after one-lung ventilation</p>	<ol style="list-style-type: none"> 1. Apply “recruitment maneuver of the ventilated lung(s)” 2. Increase PEEP to 12 cmH₂O and apply “recruitment maneuver of the ventilated lung(s)” 3. Increase FIO₂ in steps of 0.1 until 1.0 4. Consider stepwise decrease of PEEP of the ventilated lung down to 8 cmH₂O
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<p>Hypoxemia Rescue - LOW PEEP GROUP - before and after one-lung ventilation</p>	<ol style="list-style-type: none"> 1. Increase FIO₂ in steps of 0.1 until 1.0 2. Apply “recruitment maneuver of the ventilated lung(s)” 3. Increase PEEP to 6 cmH₂O 4. Apply “recruitment maneuver of the ventilated lung(s)” 5. Increase PEEP to 7 cmH₂O 6. Apply “recruitment maneuver of the ventilated lung(s)”
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<p>Hypoxemia Rescue - HIGH PEEP GROUP - during one-lung ventilation</p>	<ol style="list-style-type: none"> 1. Apply “recruitment maneuver of the ventilated lung(s)” 2. Increase PEEP to 12 cmH₂O and apply “recruitment maneuver of the ventilated lung(s)” 3. Increase FIO₂ in steps of 0.1 up to 1.0 4. Apply oxygen to the non-ventilated lung, consider CPAP therapy (Recruitment maneuver of the non-ventilated lung) up to a pressure of 20 cmH₂O or selective oxygen insufflation via fiberoptic 5. Consider stepwise decrease of PEEP of the ventilated lung down to 8 cmH₂O 6. Consider surgical intervention (e.g. clamping of the pulmonary artery) 7. Consider administration of inhalative nitric oxide or prostacyclin, or intravenous almitrin 8. Switch to TLV
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<p>Hypoxemia Rescue – LOW PEEP GROUP - during one-lung ventilation</p>	<ol style="list-style-type: none"> 1. Increase FIO₂ in steps of 0.1 up to 1.0 2. Apply oxygen to the non-ventilated lung, consider CPAP therapy (Recruitment maneuver of the non-ventilated lung) up to a pressure of 20 cmH₂O or selective oxygen insufflation via fiberoptic 3. Apply “recruitment maneuver of the ventilated lung(s)” 4. Increase PEEP to 6 cmH₂O 5. Apply “recruitment maneuver of the ventilated lung(s)” 6. Increase PEEP to 7 cmH₂O 7. Apply “recruitment maneuver of the ventilated lung(s)” 8. Consider surgical intervention (e.g. clamping of the pulmonary artery) 9. Consider administration of inhalative nitric oxide or prostacyclin, or intravenous almitrin 10. Switch to TLV
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6.4.5 Hypercapnia Rescue therapy

Hypercapnia Rescue – BOTH GROUPS - during one-lung ventilation

If hypercapnia ($\text{PaCO}_2 > 60 \text{ mmHg}$) with respiratory acidosis ($\text{pHa} < 7.20$) occurs during OLV, follow steps will be applied in both the high and low PEEP groups:

<p>Hypercapnia Rescue – BOTH GROUPS - during one-lung ventilation</p>	<p>$\text{PaCO}_2 > 60 \text{ mmHg}$ with respiratory acidosis ($\text{pHa} < 7.20$)</p> <ol style="list-style-type: none"> 1. Increase the respiratory rate (maximum 30/min, while avoiding intrinsic-PEEP) 2. Increase V_T in steps up to 7 mL/kg 3. Switch to TLV
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6.5 Standard procedures

Start of surgery will be defined as the moment of incision for open surgery or insertion of trocars for thoracoscopic surgery. End of surgery is the moment of closure of the surgical wound.

Routine general anesthesia, post-operative pain management, physiotherapeutic procedures and fluid management will be performed in the intra-operative and/or post-operative period according to each center's specific expertise and clinical routine. However, the following procedures are suggested:

- To use inhalational isoflurane, desflurane or sevoflurane, intravenous propofol, remifentanil or sufentanil, and cis-atracurium, atracurium, vecuronium, or rocuronium (as required)
- To use sugammadex or a balanced solution of prostigmine, or neostigmine and atropine or glycopyrrolate for reversal of muscle relaxation, guided by neuromuscular function monitoring (for example train-of-four)
- To perform postoperative pain management in order to achieve a VAS pain score below 3. Use of regional anesthesia, including epidural, paravertebral and intercostal blockade, and taking indications, contra-indications and local preferences into account is encouraged, but not obligatory
- To use physiotherapy by early mobilization, deep breathing exercises with and without incentive spirometry and stimulation of cough in the postoperative period
- To avoid fluid under and overload (at discretion of the anesthesiologist)
- To use invasive measurement of arterial blood pressure whenever indicated
- To use appropriate prophylactic antibiotics whenever indicated
- To use gastric tubes, urinary bladder catheters, and more invasive monitoring according to individual needs, as well as local practice and/or guidelines

Other procedures should follow the Safe Surgery Checklist (see www.who.int/patientsafety/safesurgery/en/index.html).

6.6 Data to be collected

Preoperative variables and consent will be collected before surgery (Investigator 1 or 2). Intraoperative variables will be collected during surgery (Investigator 1). Postoperative variables will be collected on the postoperative day 1 to 5, on the day of discharge from hospital as well as on day 28 and day 90 after trial enrollment (Investigator 2).

A comprehensive CRF will guide each investigator through the process of data acquisition. Look for the corresponding file (CRF_PROTHOR.doc).

Pre-operative variables

Pre-operative variables will be collected at the pre-anesthetic visit or before induction of general anesthesia:

- Gender and age; male + years
- Height and weight; kg + cm
- ARISCAT Score
- **History of previous disease**
 - Physical status; according to the American Society of Anesthesiologists (ASA)
 - Cumulated Ambulation Score 26 (CAS) to evaluate mobility
 - Metabolic equivalents
 - Cardiac status: heart failure, according to the New York Heart Association (NYHA); coronary heart disease, according to Canadian Cardiovascular Society Classification (CCS), atrial flutter/fibrillation
 - In patients without known obstructive sleep apnea (OSA), STOP-Bang score
 - In patients with known OSA, apnea-hypopnea index (AHI)
 - COPD with inhalation therapy and/or steroids; if yes: specify
 - Respiratory infection in the last month; if yes: specify upper or lower respiratory infection
 - Smoking status; never, former (at least three months prior) or current
 - Use of noninvasive respiratory support; if yes: specify if CPAP or NPPV, duration and intensity

- History of active cancer; if yes, specify type of cancer, classification + therapy; chemotherapy in last 2 months
 - History of diabetes mellitus; if yes: dietary treatment, oral medication or insulin therapy
 - History of hypertension
 - History of gastroesophageal reflux disease
 - Alcohol status in the past 2 weeks; 0–2 drinks/day or > 2 drinks/day
 - Use of antibiotics in the last 3 months; if yes: specify indication + drug
 - Use of statins; if yes: specify type and dose
 - Use of aspirin; if yes: specify dose
- **Actual organ function evaluation**
 - SpO₂ in supine position with upped body elevated (30-45°), 10 minutes in room air. if not possible amount of oxygen needed
 - Respiratory rate
 - Heart rate; BPM
 - Noninvasive mean arterial pressure; mmHg
 - Body temperature; °C
 - Airway secretion score: ask patient to cough and subjectively evaluate presence and consistency of sputum; if yes: purulent or not
 - Visual Analogue Scale (10 cm): evaluation for dyspnea, thoracic rest and coughing pain
 - if available chest x-ray and findings of infiltrates, pleural effusions, atelectasis, pneumothorax, cardiopulmonary edema (no x-ray due to study requirements , only if clinically indicated)
 - CT data/radiologic images of study patients are collected in a database (if collaboration with radiology permits at no/low cost)
 - laboratory tests of hemoglobin, white blood cell count, hematocrit, creatinine, blood urea nitrogen, platelets, prothrombin time and international normalized ratio, partial thromboplastin time, alanine aminotransferase, aspartate aminotransferase, bilirubin, c-reactive protein, procalcitonin
- **preoperative lung variables**
 - arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide, pH value, forced vital capacity (FVC), forced expiratory volume at 1 second

(FEV1), tiffeneau index, total lung capacity, diffusing capacity for carbon monoxide (DLCO), maximal oxygen consumption, predicted postoperative values for FVC, FEV1, DLCO

Intra-operative variables

During the intra-operative period, the following variables will be recorded (variables are to be measured after induction, after start of surgery and prior to OLV, 10 minutes after the start of OLV, 1 hour after the start of OLV, every hour after the start of OLV; end of surgery with two lung ventilation in supine position):

- **Randomization result**
- **Anaesthetic Overview**
 - Duration of anesthesia procedure; from tracheal intubation to extubation or exit from operation room (in case patient remains on mechanical ventilation); minutes
 - Duration of TLV; cumulative, minutes
 - Duration of OLV; cumulative, minutes
 - Blood loss; ml for whole duration of surgery
 - Urine output; ml for whole duration of surgery
 - Side of surgery and of OLV
 - Method of OLV (choose from double lumen tube, endobronchial blocker, double lumen tube with embedded camera or specify if other)
 - Confirmation of OLV /choose from (fiberoptic bronchoscopy, embedded camera or specify if other)
 - Antibiotic prophylaxis; if yes: specify regimen
 - Use of regional anesthesia if yes specify type (epidural, paravertebral, or specify if other)
 - Use of non-invasive ventilation during induction (if yes specify type (CPAP, NPPV))
 - Patients position during induction (specify angle of upper body elevation)
 - Temperature at end of surgery °C
 - Monitoring of neuromuscular function at end of surgery (if yes specify train of four value), need for curarisation antagonists(specify type: sugammadex, cholinesterase inhibitors, or specify of other)
- **Surgical overview**
 - Duration of surgery
 - Priority of surgery (elective, urgent, emergency)
 - Surgical wound classification (clean, clean-contaminated, contaminated, dirty)

- Surgical procedure (thoracoscopic, open, conversion to open)
- Type of resection (pneumonectomy, lobectomy, wedge resection, sleeve lobectomy, segment resection, pleurectomy, specify if other)
- Patients position during surgery (supine, lateral, prone, specify if other)
- Estimated amount of resection (specify amount in %)
- **Anesthesia Drugs**
 - Analgetics
 - Anesthetics
 - Muscle relaxants
 - Vapors (specify mean targeted MAC during surgery)
- **Fluids**
 - Crystalloids, albumin, artificial colloids (specify type and amount)
 - Vasoactive drugs
- **Transfusion**
 - Packed red blood cells, autologous blood transfusion, plasma, platelets (specify cumulative amount)
- **Protocol adherence**
 - Hypotension (BP_{sys} < 90mmHg) unresponsive to fluids and/or vasoactive drugs
 - New arrhythmias unresponsive to intervention (according to ACLS-Guidelines)
 - Need for a dosage of vasoactive drugs at the tolerance limit
 - Need of massive transfusion (4 units of PRBC in 4 hours)
 - Life-threatening surgical complication (injury to the hemodynamic and respiratory system and brain, including major bleeding, tension pneumothorax, intracranial injury)
 - Rescue for hypoxemia (prolonged SpO₂ < 90%); rescue steps should be specified (e.g. “Rescue for hypoxemia was necessary; only once; no further rescue was required”)
 - Rescue for hypercapnia (PaCO₂ > 60 mmHg) with respiratory acidosis; rescue steps should be specified (e.g. “Rescue for hypercapnia/resp. acidosis was necessary; only once; no further rescue was required”)
 - Deviation from prescribed PEEP
 - Deviation from prescribed tidal volume
 - Other reason, specify
- Adverse Events
- Intraoperative variables

- Time of measurement, if on TLV or OLV, peak pressure, plateau pressure, PEEP, tidal volume, respiratory rate, I:E ratio, FiO₂, SpO₂, endtidal CO₂, mean arterial pressure, heart rate, arterial oxygen partial pressure, arterial CO₂ partial pressure, hematocrit, events of new hypotension, new bradycardia, new hypoxemia, disconnection from ventilator, hypoxemia rescue maneuver, hypercapnia rescue maneuver, use of inhalation NO or prostacyclin or selective fiberoptic insufflation, CPAP therapy of the non-ventilated lung or specify other events).
- Intraoperative signals (for participating centers only)
 - Recordings of respiratory and haemodynamic signals in high temporal resolution (sampling rate > 10 Hz): airway flow, volume and pressure (as measured by the anesthesia machine: Dräger Primus) and electrocardiogram and, if available, continuous invasive airway pressure (routine patient monitoring system: Philips MP70). All signals are recorded online using a certified communication port without additional hardware.

Post-operative variables

The patients will be assessed daily between the first and the fifth day after surgery as well as on the last day before discharge from hospital, as well as on day 28 and day 90 after randomization by telephone. Clinical data and the presence of pulmonary and extra-pulmonary postoperative complications will be scored, the date of development of any complication documented (for definitions, see APPENDIX).

- **Recovery**
 - Is the patient lost to follow up?
 - Continuation of non-invasive or invasive mechanical ventilation outside of the operation room directly after surgery; if yes: specify indication and duration, hours; an “unplanned” MV will be considered as a PPC. This will be recorded together with the indication.
 - Any new requirement of non-invasive CPAP or NPPV; if yes: specify indication, duration and intensity
 - Any new requirement of invasive mechanical ventilation; if yes: specify indication, duration and intensity
 - ICU stay directly postoperative; if yes: specify reason; specify whether it was planned or not
 - Any new admission or readmission to the ICU at any time in the post-operative period; if yes: specify reason

- Physiotherapy and breathing exercises
 - CAS to evaluate mobility
 - Wound healing: impaired wound healing can be defined as an interruption in the timely and predictable recovery of mechanical integrity in the injured tissue
 - Surgical wound infection; if yes: specify location (superficial or deep, abscess, empyema or phlegmon)
 - Antibiotic therapy, specify if therapeutic or prophylactic indication
 - Postoperative nausea and vomiting (PONV)
 - Return of bowel function
- **Fluids and transfusion on Day 1**
 - Record all fluids that have been administered within the first 24 hours from the end of anesthesia or if the patient remained mechanically ventilated, from exiting the OR; Crystalloids, Colloids, Albumin, specify amount; also specify cumulative dose of vasoactive drugs
 - Record all blood products that have been administered within the first 24 hours from the end of anesthesia or if the patient remained mechanically ventilated, from exiting the OR; packed red blood cells, plasma, platelets, autologous blood transfusion; specify cumulative amount
- **Actual organ function**
 - SpO₂ in supine position with upper body elevated (30-45°), 10 minutes in room air. if not possible amount of oxygen needed
 - Respiratory rate
 - Heart rate; BPM
 - Noninvasive mean arterial pressure; mmHg
 - Body temperature; °C
 - Airway secretion score: ask patient to cough and subjectively evaluate presence and consistency of sputum; if yes: purulent or not
 - Visual Analogue Scale (10 cm): evaluation for dyspnea, thoracic rest and coughing pain
 - **Non mandatory measurements**
 - if available chest x-ray and findings of infiltrates, pleural effusions, atelectasis, pneumothorax, cardiopulmonary edema (no additional x-ray required by study protocol; only if clinically indicated)
 - CT data/radiologic images of study patients are collected in a database (if collaboration with radiology permits at no/low cost)

- laboratory tests of hemoglobin, white blood cell count, hematocrit, creatinine, blood urea nitrogen, platelets, prothrombin time and international normalized ratio, partial thromboplastin time, alanine aminotransferase, aspartate aminotransferase, bilirubin, c-reactive protein, procalcitonin
- **Pulmonary complications; extended pulmonary complications; extrapulmonary complications**
- **Blood samples** (for participating centers only)

Before and at the end of surgery, as well as for the following 5 days, blood samples (10 ml) will be collected in case that the patient has an established vascular access that permits easy blood sampling. The blood samples are stored at minus 80°C for measurement of:

 - Inflammatory mediators (e.g. cytokines, chemokines, other inflammatory proteins)
 - Markers of lung injury (e.g. angiopoietin-2, surfactant proteins A and D)
 - Specific markers of distal organ injury (e.g. cystatin C, NGAL)
- **Bronchoalveolar sampling** (for participating centers only)

Confirmation of double lumen tube position is done by fiberoptic bronchoscopy. During surgery we will acquire a tracheobronchial probe by means of fiberoptic bronchoscopy. In the case, that a patient has postoperative unplanned invasive ventilation (intensive care unit), a tracheobronchial probe will be acquired daily by means of fiberoptic bronchoscopy. To facilitate probe acquisition, injection of saline solution (0,9%) may be necessary.
- **Discharge**
 - Event of death
 - Date of discharge, day of discharge since randomization, discharge destination (home, other hospital/care, death)
- **Followup**
 - Alive hospital free days at day 28
 - Alive at day 90 after study inclusion

6.7 Visits

	Preoperative	Intraoperative	Postoperative day 1	Postoperative day 2	Postoperative day 3	Postoperative day 4	Postoperative day 5	Discharge	Day 28	Day 90
Inclusion Criteria	x									
Exclusion Criteria	x									
ARISCAT Score	x									
History of previous disease	x									
Actual organ function	x		x	x	x	x	x	x		
Non-mandatory measurements	x		x	x	x	x	x	x		
Preoperative lung variables	x									
Randomization		x								
Anaesthetic Overview		x								
Surgical overview		x								
Anesthesia Drugs		x								
Fluids		x	x							
Transfusion		x	x							
Protocol adherence		x								
Adverse Events		x								
Intraoperative routine measurements		x								

Intraoperative recruitment maneuvers		x								
Recovery			x	x	x	x	x	x		
Pulmonary complications			x	x	x	x	x	x		
Extrapulmonary complications			x	x	x	x	x	x		
Discharge								x		
Followup									x	x

7 STATISTICAL ANALYSIS

7.1 Descriptive statistics

Patient characteristics will be compared and described by appropriate statistics.

7.2 Analysis

Normally distributed variables will be expressed by their mean and standard deviation; non-normally distributed variables will be expressed by their medians and interquartile ranges. Categorical variables will be expressed as n (%).

Student's t-test will be used to test groups of continuous normally distributed variables. Conversely, if continuous data is non-normally distributed, the Mann-Whitney U test will be used. Categorical variables will be compared with the Chi-square test, Fisher's exact tests or, where appropriate, as relative risks. Time dependent data will be analyzed using a proportional hazard model adjusted for possible imbalances of patients' baseline characteristics. Statistical significance is considered to be at a p-value of 0.05. Where appropriate, statistical uncertainty will be expressed by 95% confidence levels.

8 ADVERSE EVENTS

8.1 Definition

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding) syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention. With respect to intensity, adverse events are classified as follows:

- Mild some awareness of symptoms, but easily tolerated;
- Moderate symptoms causing enough discomfort to interfere with usual activity;
- Severe incapacitating event causing inability to work or to perform usual activity.

Adverse events are classified as either serious or non-serious:

A **Serious Adverse Event (SAE)** is defined as any experience that suggests a significant hazard or side-effect with respect to participants participating in a clinical study. This includes any experience which:

- is fatal or life-threatening,
- is permanently disabling, i.e. incapacitating or interfering with the ability to resume normal life patterns,
- requires hospitalisation or prolongation of hospitalisation,
- is a congenital anomaly or defect,
- other medically important circumstance (requires medical treatment to avoid one of the above mentioned conditions).

Participation in the study is defined as time from randomization until last day of follow up (90 days after randomization)

8.2 Documentation

All adverse events have to be documented in the CRF. Cases of misuse, or deviations in the administration of the study therapy have to be documented even when there is no adverse event. In cases where the AE results in a persistent disease, the AE has to be classified as a SAE and will be documented as such at the end of the trial.

8.3 Data Safety Monitoring Board (DSMB)

The DSMB will be composed of five individuals, one of whom will be the chairperson.

- The DSMB will convene after a specified number of patients, listed in the sample size calculation chapter.

- All adverse events will be reported to the DSMB for review. All serious events will be reported within 24 hours after being received by the coordinating center. Non-serious events will be reported within one week of reception by the coordinating center
- All unexpected study-related or possibly study-related adverse events will be reported to the DSMB. Adverse events include, but are not limited to unexpected death, inadvertent extubation, development of hemodynamic compromise during a recruitment maneuver or PEEP adjustment, sudden hypoxemia, hypercarbia or a pneumothorax during changes in ventilator setting in either the control or treatment group.
- The DSMB will monitor the overall status of the trial: number of patients enrolled overall and per each center, adherence to protocol overall and per center and results of the interim analysis.

The DSMB includes the following individuals:

1. Daniel Sessler, Cleveland, USA (CHAIR)
2. Arthur Slutsky, Toronto, Canada
3. Claudia Spies, Berlin, Germany
4. Jean-Louis Vincent, Brussels, Belgium
5. Jennifer Hunter, Liverpool, Great Britain

8.4 Withdrawal of study participants

Participation in the trial is voluntary. A subject has the right to withdraw from the study at any time for any reason without any consequences for the further medical treatment. If s/he chooses to withdraw, the investigator will be informed immediately.

Furthermore, the investigator has the right to terminate the participation of any subject at any time, if s/he deems it in the participant's best interest.

The reason and circumstances for study discontinuation will be documented in the participant's CRF.

8.5 Risk Benefit Assessment

OLV is a common method of anaesthesia in the field of lung surgery. The difficulty in choosing the right level of PEEP is the responsibility of the treating physician. Also, the varieties of manoeuvres that can be used to treat hypoxemia and hypercarpna, which are common in OLV, are numerous. The steering committee, assembled from leading experts in thoracic anaesthesia, was charged to design simple and safe manoeuvres to manage the challenges of thoracic surgery. The implementation of the study protocol relies on standardized procedures. Individual experience of the treating physicians may influence the safety of the patient. Uncommon manoeuvres may not be clear at first sight and can lead to delayed treatment effect. On the other hand, physicians may profit from the expert knowledge that underlie the interventional protocol. Novel treatment methods may enrich the physicians' portfolio of medical interventions.

The patient is monitored continuously during the intervention. The intervention itself is far from being experimental, more or less representing standard of care in individual hospitals. All ventilators and drugs are licensed and used according to every day practise. The treating physician is encouraged to follow the study protocol, but can deviate from the protocol if the safety of the patient is at risk. Blood examinations and radiographic images will not be performed for study purposes only. The study will access results from tests performed for clinical purposes.

In conclusion, the patient is not known to be at increased risk during the study compared to standard care, provided the treating physician is well trained and familiar with the study protocol. The patient may profit from intensified monitoring during the postoperative visits, which may enhance the patient's safety.

8.6 Responsibilities of the investigator

The clinical investigator assures that the clinical study is performed in accordance with:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996,
- Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended To-kyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh, 2000),

This study must be carried out in compliance with the protocol. The responsibilities of the investigator include:

- execution of the treatment plan,
- sufficient time and capacity to perform the clinical study,
- correct collection and documentation of study related data and reporting,
- provision of data for audits/inspections,
- ensuring strict confidentiality and requesting similar confidentiality from her/his staff concerning information about participants. Study documents provided by the study director (protocols, Investigator's Brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the study director to the investigator may not be disclosed to others without direct written authorization from the study director, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial,
- providing financial disclosure.

The clinical investigator has full responsibility for the conduct of the clinical study in the study center.

9 ADMINISTRATIVE ASPECTS AND PUBLICATION

9.1 Documentation

It is the responsibility of the investigator to perform the clinical study in accordance with the GCP guidelines and the clinical study protocol. All data have to be recorded correctly in the CRF by authorized persons only. This also includes data of persons that were excluded from the clinical study.

All data of the participants have to be recorded in the CRF. The Investigator is responsible for all data of the participant to be documented in the CRF exclusively designed for the study immediately, correctly and completely.

Corrections in the CRF are to be conducted only by authorized personnel and are to be justified. The former database entry must stay retrievable. All dates and corrections are recorded automatically concerning date, time point and person.

9.2 Handling and storage of data and documents

All enrolled patients identification data will be pseudonymized. The codebook has to be stored separately.

All documents that are related to the clinical study (e.g. CRFs, written informed consent forms, and other relevant material) have to be stored as long as requested by local law.

Source data like patients' charts, laboratory analyses, and other original data have to be stored for the longest possible time that is usual practice at the investigator's site.

9.3 Publication policy

The results of this trial will be published. In all publications the confidentiality of patients' data has to be ensured. The study will be registered in a data base that is accessible to the public. By signing this study protocol, the investigators accept that the results of this trial can be presented to national and international authorities. They also accept that in this context their name, address, qualification and grade of involvement in this trial will be published.

The trial is planned to be published under the authorship of "The PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology", in accordance with the policy of the PROVE Network.

Collaborators of the trial will be listed as collaborating authors/network investigators. Each participating institution will be granted one co-authorship per 20 randomized patients who are included in the analysis.

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APPENDIX

Please refer to the file entitled "appendix.docx"

CHANGELOG

Changes from Version 2.1 compared to Version 2.0

Update of the Steering committee and DSMB. Correction of spelling mistakes.