Clinical Study Protocol

PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after THORACic surgery – an international multicenter *pilot* randomized clinical trial

SHORT TITLE: PROFLOW–THORACic *pilot*

Type of study:	Other Clinical Trial according to ClinO, Chapter 4.
Study Risk Categorization:	Risk category A according to ClinO, Art. 61.
Study Registration:	The trial was registered at clinicaltrials.gov (NCT07623395) and the Swiss Human Research Portal (___). Registration was done after receipt of the approval from the Competent Ethics Committee and prior to start of the trial.
Study Intervention:	Flow–controlled ventilation
Control intervention:	Volume–controlled ventilation
Study Identifier:	CTU S26.006 EKOS 2026-01105; BASEC No.: 2026-01105
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Study Short Title:	PROFLOW–THORACic *pilot*
Version and Date:	Version 1.0, 15.05.2026

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PROTOCOL SIGNATURE FORM

Study identifier: CTU S26.006; EKOS 26/097

Study Title: PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after THORACic surgery – an international mutli-center *pilot* randomized clinical trial.

The Sponsor has approved protocol Version 1.0, 15.05.2026 and confirms hereby to conduct the investigation according to the protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH–GCP guidelines, and the local legally applicable requirements.

Sponsor: Department of Anaesthesiology, Rescue– and Pain Medicine, HOCH Health Ostschweiz, Cantonal Hospital St. Gallen, Switzerland



15.05.2026

Date | Signature

Statistician: not assigned yet

Date | Signature

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ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ANOVA	Analysis of Variance
ARDS	Acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
ASR	Annual Safety Report
AUC	Area under the curve
BMI	Body mass index
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV)*
COPD	Chronic obstructive pulmonary disease
CoV	Center of ventilation
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
CTU	Clinical Trials Unit
DLT	Double Lumen Tube
EELV	End expiratory lung volume
EELI	End expiratory lung impedance
EIT	Electrical Impedance Tomography
FCV	Flow-controlled ventilation
FEV1	Forced expiratory volume
FRC	Functional residual capacity
GI index	Global inhomogeneity index
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG)*
ICF	Informed Consent Form
ICU	Intensive care unit
ID	Inner Diameter
ISF	Investigator Site File
ITT	Intention to treat
OLV	One–lung ventilation
PACU	Post–anesthesia care unit
PEEP	Positive end–expiratory pressure
PI	Principal Investigator
PIP	Positive inspiratory pressure
POD	Postoperative day
PPC	Postoperative pulmonary complications
ROI	Region of interest
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TLV	Two Lung Ventilation
VCV	Volume–controlled ventilation
VILI	Ventilator induced lung injury

STUDY SYNOPSIS

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Title:	PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after THORACic surgery – an international multicenter *pilot* randomized clinical trial.
Short title / Study ID:	PROFLOW–THORACic *pilot* / CTU S26-006
Protocol version and date:	Version 1.0, 15.05.2026
Registration:	The study is registered at clinicaltrials.gov (NCT07623395) and the Swiss Human Research Portal (___). Registration was done after receipt of the approval from the Competent Ethics Committee and prior to start of the trial.
Category and its rationale:	In an international multicenter randomized clinical *pilot* trial, intraoperative flow–controlled ventilation (FCV) will be compared with volume–controlled ventilation (VCV) in patients scheduled for (open, video– or robot–assisted) thoracic surgery with one–lung ventilation (OLV). This *pilot* trial is designed to test the feasibility and safety of FCV during all phases of intraoperative ventilation, and in particular during OLV, and to inform the design of a future trial testing the efficacy of FCV with regard to postoperative outcomes, including postoperative pulmonary complications (PPC). The ventilation modes are conducted with CE–marked medical devices (anesthesia ventilators or medical ventilators), however these medical devices themselves are not under investigation. All CE–marked standard medical devices from varied manufacturers in use at the participating study centers will be used in full accordance with their instructions for use. FCV has shown safety and feasibility in various surgical settings, including thoracic surgery with OLV, however its feasibility in a multicenter trial has not been investigated yet. Without further investigation planned, the additional risk and burden for the participants of this trial is considered as minimal, resulting in a risk category A according to ClinO, Art. 61.
Background and rationale:	Optimizing intraoperative ventilation, i.e., to ensure adequate gas exchange and guarantee safe carbon dioxide elimination, is crucial in patients under general anesthesia, where physiologic breathing is replaced by artificial ventilation. Altered respiratory compliance and impaired gas exchange complicate management, particularly during thoracic surgery with OLV. Compared to abdominal surgery, intraoperative ventilation during OLV for thoracic procedures carry a higher risk for PPCs. The challenges are most pronounced during the OLV phase, where a careful balance must be achieved between providing sufficient ventilation for adequate gas exchange and protecting the lung. Intraoperative lung–protection strategies have steadily improved in recent years to reduce complications from mechanical ventilation, but PPC remain a risk factor for increased morbidity and mortality. This *pilot* trial will be conducted to evaluate the feasibility and safety of intraoperative FCV during all phases of intraoperative ventilation, but in particular during OLV for open, video– or robot–assisted thoracic surgery. It will inform the design of a future trial that will test the efficacy of intraoperative FCV compared to VCV in these patients, with an additional aspect to investigate sex differences between ventilation strategies.

Risk / Benefit Assessment	FCV has demonstrated beneficial physiologic effects in small–sized animal and human studies, with one human study focusing on thoracic surgery and OLV. In summary, these trials have primarily focused on ventilation or gas exchange parameters. However, multicenter studies are needed to assess the feasibility and safety of FCV, particularly in patients undergoing OLV for thoracic surgery, to guide the design of larger randomized clinical trials evaluating its impact on patient outcomes. As recent trials in FCV have reported no major risks for the patients, we consider the investigation to be safe and due to the potential of an impact on the reduction of PPC as important to conduct this trial. The here proposed international multicenter randomized clinical *pilot* trial will be conducted to test the feasibility and safety of FCV (as well as the ventilation protocol for the comparator group VCV), and its findings will be used to inform the design of a future trial testing the efficacy with regard to PPCs.
Hypotheses	FCV is a feasible and safe during OLV in patients undergoing (open, video– or robot–assisted) thoracic surgery; the study protocol is feasible.
Objective(s):	The primary objective of this *pilot* study is to assess the feasibility of the *ventilation* protocols (see section 9. Study Procedures) for intraoperative FCV and VCV during the entire period of intraoperative ventilation, with particular attention to the period of OLV, in patients undergoing thoracic surgery. Secondary objectives are to evaluate the safety of these *ventilation* protocols, the feasibility of the *study* protocol, and the effect of FCV compared to conventional ventilation on key endpoints that will be used in a larger follow–up study. • feasibility of the ventilation protocols includes whether both modes can be applied during all phases of intraoperative ventilation, in particular during OLV, achievement of key ventilator settings and ventilation parameters, and the surgeon's assessment of how the mode of ventilation affects surgical conditions; • safety covers aspects of gas exchange, including unacceptable deviations in oxygenation and decarboxylation, respiratory complications such as pneumothorax; hemodynamic complications such as hypotension and arrhythmias; and the need for rescue ventilation strategies; • feasibility of the study protocol includes compliance with the ventilation protocols, missing perioperative data in the eCRF, and the practicality of capturing intraoperative and postoperative variables and postoperative outcomes; and • PPC will be captured for the first seven postoperative days, and this analysis will be explorative.

Outcome(s) and Measurements Procedures:	Outcomes in this *pilot* study are selected to support the evaluation of feasibility and safety of the *ventilation* protocols used, *study* protocol integrity, and to inform the design of the larger follow-up study. The primary outcome of this *pilot* study is a composite of feasibility issues of the ventilation protocols, including • correct use of predefined standard ventilator settings (with both modes); • correct titration of PEEP and driving pressure (with FCV), and correct PEEP and tidal volume (with VCV); • correct titration of FiO_2 (with both modes); • correct respiratory monitoring (with both modes); • any significant deviation from the predefined standard ventilator settings (with both modes), PEEP and driving pressure titrations (with FCV) and PEEP and tidal volume (VCV) beyond pre-approved deviations for safety; and • any significant deviation in ventilator settings based on surgeon's assessment of surgical conditions. Secondary outcomes of this *pilot* focus are related to safety of the ventilation protocols, feasibility of the *study* protocol, and the effect of FCV on the incidence of PPCs, all meant to advance and confirm safety and feasibility of the ventilation strategies, and the suitability of the study protocol before proceeding with the main study. For safety: • unacceptable intraoperative measures of gas exchange (hourly PaO_2 and $PaCO_2$ measurements, and continuous SpO_2 and end–tidal CO_2 readings); • unacceptable low minute ventilation; • unacceptable ventilator parameters (tidal volume, driving pressure and mechanical power of ventilation); • intraoperative pulmonary complications, such as severe atelectases and pneumothorax; and • intraoperative hemodynamic complications, such as unexpected hypotension or need for high dosages of vasopressors, arrhythmias that need an intervention. For study protocol feasibility: • proper handling of the regulatory aspects of the study, including correct enrollment of patients and correct randomization; • adherence to the study protocol, including, relevant ventilation strategy-related aspects; and relevant aspects not related to ventilation; and • correct and complete collection of intraoperative and postoperative variables and outcomes. Regarding postoperative pulmonary complications up to the 7th postoperative day: • a composite of PPCs as defined in previous studies ('PRECISION').[13]

Design:	International multicenter randomized clinical *pilot* trial.
Inclusion / exclusion criteria:	Inclusion criteria: • aged ≥ 18 years; and • scheduled for elective open, video– or robot–assisted thoracic surgery with one-lung ventilation using a double-lumen tube (DLT); and • able to give written informed consent. Exclusion criteria: • body weight < 40 kg; • ASA score IV – VI; • lung separation with other method than DLT (e.g. difficult airway, tracheostomy); • previous lung surgery; • 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; • documented pulmonary arterial hypertension >25 mmHg mPAP at rest or >40mmHg syst. (estimated by ultrasound) or >20 mmHg mPAP measured by right heart catheterization, or pulmonary vascular resistance > 2.0 Wood units; • documented or suspected neuromuscular disease (thymoma, myasthenia, myopathies, muscular dystrophies, others); • planned mechanical ventilation after surgery; • bilateral procedures; • surgery in prone position; • persistent hemodynamic instability, intractable shock; • intracranial injury or tumor; • esophagectomy, pleural surgery only, sympathectomy surgery only, chest wall surgery only, mediastinal surgery only, lung transplantation; • presence before induction of anesthesia of one of the adverse events, listed as postoperative pulmonary complications (aspiration, moderate respiratory failure, infiltrates, pulmonary infection, atelectasis, cardiopulmonary oedema, pleural effusion, pneumothorax, pulmonary embolism, purulent pleuritis, lung hemorrhage); • documented preoperative hypercapnia > 45mmHg (6kPa) • previous enrolment in the current study; • being the study investigator of this study, his/her family members, employees and other dependent persons; • if female and of childbearing potential, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating; or • no written informed consent.
Intervention:	Flow–controlled ventilation.
Control intervention:	Volume–controlled ventilation (current best practice & standard of care).
Study procedures:	Intraoperative ventilation strategy with individualized FCV with dynamic compliance guided titration of PEEP and driving pressure during all phases of intraoperative ventilation compared to an intraoperative ventilation strategy with current best practice lung protective VCV with standard PEEP.

Number of subjects with rationale:	To estimate the appropriate sample size for this *pilot* trial, we considered both feasibility and safety across multiple centers. Assuming a target of 10 participants per randomization group in each of the centers, the total sample size would include 140 participants (7 centers × 10 participants × 2 randomization groups). The rationale of this number is based on previous (and ongoing) pilot studies of FCV and balances logistical feasibility with the need for adequate data to assess safety outcomes.
Duration of study:	18 months from start of screening of patients to end of inclusion and statistical analysis.
Study schedule:	First–Patient–First–Visit: Q3 2026 (planned) Last–Patient–Last–Visit: Q3 2027 (expected) End-of-Trial: Q4 2027
Study Sites:	• Department of Anesthesiology, Rescue- and Pain Medicine, HOCH Health Ostschweiz, Cantonal Hospital St. Gallen, St. Gallen, Switzerland • Department of Anesthesia and Intensive Care Medicine, Medical University Innsbruck, Innsbruck, Austria • Department of Anesthesia and Intensive Care Medicine, Medical University Graz, Graz, Austria • Department of Anesthesiology, Intensive Care and Pain Medicine, BG University Hospital Bergmannsheil, Ruhr-University Bochum, Bochum, Germany • Department of Anesthesiology, University Hospital Düsseldorf, Düsseldorf, Germany • Department of Anesthesiology and Pain Medicine, Hopital Foch, Universite' Versailles-Saint-Quentin-en-Yvelines, Suresnes, France • Department of Anesthesiology, University of Amsterdam, Amsterdam, the Netherlands
Statistical considerations:	This *pilot* trial primarily aims to assess the feasibility of the ventilation protocols for intraoperative FCV and conventional ventilation during the entire period of intraoperative ventilation, with particular attention to the period of OLV, in patients undergoing thoracic surgery. Secondary objectives are to evaluate the safety of these ventilation protocols, the feasibility of the study protocol, and the effect of FCV compared to conventional ventilation on key endpoints that will be used in a larger follow-up study. All outcomes will be compared between sexes. The *pilot* trial is not powered to detect any impact of clinical outcomes. Descriptive analyses will be conducted, focusing on the progression outcomes of the study. The complete statistical analysis plan will be published before the database is cleaned and closed
Data privacy	The principal investigator affirms and upholds the principle of the participants' right to privacy and shall comply with applicable privacy laws. Particularly the anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. All data and exports of electronic records which will be stored on the, password protected server with access permissions/audit trail, fulfilling Good Clinical Practice (GCP), Swissethics requirements and requirements of the respective countries of each participating center and stored on a secure database server.
Ethical consideration	The aim of this *pilot* trial is to investigate the feasibility and safety of FVC (as well as the ventilation protocols for FCV & VCV) in thoracic surgery, and the feasibility of study protocol to inform the design of a future trial testing its efficacy with regard to postoperative outcomes. Given that ventilation strategies inherently carry certain risks, yet remain essential in the context of general anesthesia and surgery, it is ethically justified to first conduct a pilot trial. The potential benefits of FCV in thoracic surgery are significant and warrant investigation. Therefore, we find it appropriate to compare FCV with existing strategies such as VCV, as we anticipate meaningful improvements in patient outcomes with minimal additional risk.

	Feasibility and safety outcomes will determine whether to advance and confirm the suitability of the pilot study protocol before proceeding with the main study. Upon completion of the pilot study, these outcomes will be evaluated and reported. The main study will commence only if the pilot study confirms that FCV is as feasible as conventional ventilation during general anesthesia for this surgery. Should feasibility outcomes indicate the need for adjustments, modifications to the study protocol will be considered before continuing with the main study.
GCP statement:	This *pilot* trial will be conducted in compliance with its protocol, the current version of the Declaration of Helsinki, the ICH–GCP as applicable for the trial category, the HRA as well as other locally relevant legal and regulatory requirements.

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr., Version Date	Chapter	Description of change	Reason for the change

1. STUDY ADMINISTRATIVE STRUCTURE

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Statistician

Not assigned yet.

Monitoring institution

The Monitoring Institution for the study site St. Gallen is the Clinical Trials Unit, HOCH Health Ostschweiz, Cantonal Hospital St. Gallen, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland.

2. STEERING COMMITTEE

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3. DATA SAFETY MONITORING BOARD

Not applicable.

4. BACKGROUND AND RATIONALE

FCV differs from conventional ventilation modes in several key ways. Unlike pressure–controlled ventilation and VCV, FCV maintains a constant airflow during both the inspiration and expiration phases.[1–3] This method generates smooth linear pressure variations by delivering a constant positive flow during inspiration and a constant negative flow during expiration, resulting in linearly changing airway pressures (Figure 1).[3] Additionally, FCV operates without any interruptions in flow throughout the cycle. This consistent rate of pressure and volume change in the lungs, particularly the linear decrease in airway pressure during expiration, has been shown to improve lung recruitment. This approach may thus reduce the risk of pulmonary complications commonly associated with conventional ventilation modes.[3]

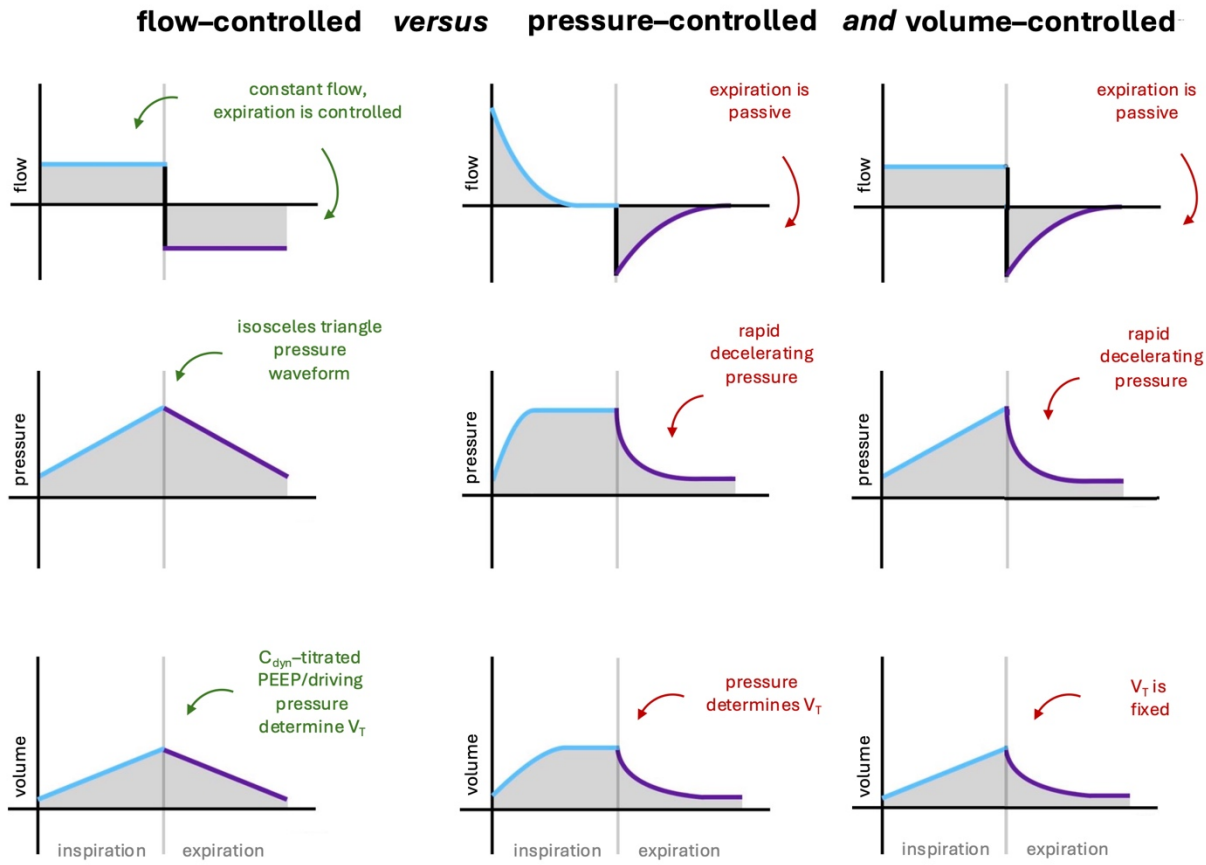


Figure 1. FCV has linear pressure, flow and volume changes in inspiration and expiration. Both VCV and PCV have variable flow and volume changes, periods with no flow and rapid pressure drops especially in exhalation. From Yurttas, et al.

Intraoperative ventilation during thoracic surgery, particularly during OLV, presents profound physiologic and clinical challenges.[4,5] When one lung is intentionally collapsed to facilitate surgical exposure, the ventilated lung must sustain the full burden of gas exchange. This abrupt reduction in functional lung volume leads to severely altered respiratory mechanics, including increased airway resistance, reduced compliance, and heterogeneous ventilation. As a result, anesthesiologists often must use high fractions of inspired oxygen (FiO_2) and perform frequent alveolar recruitment maneuvers in an effort to maintain adequate oxygenation. These strategies, however, are frequently insufficient. Persistent or recurrent atelectasis, maldistributed ventilation, and ventilation–perfusion mismatches remain common. At the same time, the need for higher airway pressures during OLV can provoke hemodynamic instability and increase the risk of VILI, especially in patients with reduced pulmonary reserve or pre–existing lung pathology.[6]

FCV has been proposed as an alternative that may mitigate some of these challenges. By actively controlling both inspiratory and expiratory flow, FCV has the potential to optimize alveolar recruitment, stabilize end–expiratory lung volume, and reduce cyclic alveolar collapse, mechanisms implicated in atelectrauma and barotrauma during OLV.[7] Early experimental and clinical evidence suggests that FCV may improve gas exchange and ventilation homogeneity under conditions of impaired lung mechanics.[8–11] Nonetheless, its application during OLV remains underexplored, and the extent to which FCV can consistently enhance intraoperative oxygenation, reduce required airway pressures, or minimize hemodynamic compromise has not been systematically studied.[12]

In recent years, intraoperative lung–protective ventilation strategies have been refined to reduce atelectasis and improve postoperative outcomes.[13–15] Despite these advances, PPCs[16] remain prevalent after thoracic surgery.[6,17] Moreover, many protective strategies rely on higher airway pressures such as sustained recruitment maneuvers or elevated PEEP, which may themselves trigger adverse hemodynamic effects.[6,13–15] Current guidelines recommend low tidal volume ventilation (6–8 ml/kg predicted body weight), although its superiority is increasingly questioned.[18] While low tidal volumes may protect against volutrauma, they may also promote atelectasis formation during OLV.[19,20]

FCV has demonstrated beneficial physiologic effects in multiple preclinical and early–phase clinical settings. Animal studies show that FCV improves lung recruitment, enhances gas exchange, promotes more uniform ventilation, and reduces inflammatory lung injury in models of acute respiratory distress syndrome.[7,9,21] Cross–over studies in healthy individuals and obese patients similarly report superior oxygenation, carbon dioxide clearance, and regional ventilation distribution compared with conventional VCV.[8,22] A single–center feasibility trial has indicated that FCV can be safely applied during OLV in thoracic surgery.[12] However, robust multi-center evidence remains lacking. Without randomized clinical trials, its feasibility, reproducibility, and potential to reduce respiratory complications compared with conventional ventilation remain uncertain. Additional feasibility and safety studies are therefore essential to guide the development of adequately powered trials and to determine whether FCV represents a meaningful advance in lung–protective ventilation during thoracic surgery. An additional focus will be laid on the differences in outcomes compared between sexes. In an ongoing pilot study investigation FCV in robot–assisted abdominal procedures, with a comparable sample size, the distribution of sexes was comparable with the recruitment phase already finished.

In summary, FCV has shown safety and feasibility, as stated, in various surgical settings, however its feasibility in a multicenter trial has not been investigated yet. As the proposed study will not include additional interventions besides the application of FCV in the intraoperative setting, the expected risks for the participants will be minimal, resulting in a risk category A, according to ClinO, Art. 61.

Therefore, this proposed international multicenter randomized clinical *pilot* trial will evaluate the feasibility and safety of FCV during all phases of intraoperative ventilation, but in particular during OLV in patients undergoing thoracic surgery.

5. STUDY OBJECTIVES

Hypotheses

FCV is a feasible and safe OLV strategy in patients undergoing (open, or video– or robot–assisted) thoracic surgery; the study protocol is feasible.

Overall objective

This *pilot* trial is designed to test the feasibility and safety of FCV during all phases of ventilation, to test the feasibility of the study protocol and electronic case report form (eCRF), to test the impact on surgical conditions, to inform the design of a future randomized clinical trial testing the efficacy of FCV with regard to postoperative outcomes, including PPCs.

Primary objective

The primary objective of this pilot study is to assess the feasibility of the ventilation protocols for intraoperative FCV and VCV during the entire period of intraoperative ventilation, with particular attention to the period of OLV, in patients undergoing thoracic surgery. All objectives will be compared between sexes.

Herein we focus on:

- the feasibility of the ventilation protocols includes whether both modes can be applied during all phases of intraoperative ventilation, in particular during OLV; and
- the achievement of key ventilator settings and ventilation parameters; and
- the surgeon's assessment of how the mode of ventilation affects surgical conditions.

Secondary objectives

Secondary objectives are to evaluate the safety of these *ventilation* protocols, the feasibility of the *study* protocol, and the effect of FCV compared to conventional ventilation on key endpoints that will be used in a larger follow–up study. All objectives will be compared between sexes.

Herein we focus on:

- safety aspects of that require the need for rescue ventilation strategies based on unacceptable measures of gas exchange, respiratory complications; hemodynamic complications; and
- feasibility of the study protocol includes compliance with the ventilation protocols, omissions in the eCRF, and the practicality of capturing intraoperative and postoperative variables and postoperative outcomes; and
- PPCs, the primary endpoint of the main study that will follow this pilot study, will be captured for the first seven postoperative days, and this analysis will be explorative.

6. STUDY OUTCOMES

Primary Outcome

The primary outcome of this *pilot* trial is a composite of feasibility* issues of the ventilation protocols, including:

- correct and complete use of the assigned ventilation strategy (with both modes) during all phases of intraoperative ventilation, and in particular OLV, i.e., adherence to the several steps of ventilation strategy (i.e., compliance-guided titration in FCV; settings according to the ventilation protocol described in section 9.);
- correct use of predefined standard ventilator settings (with both modes) (see; Section 9. 'Study Procedures';
- correct titration of PEEP and driving pressure (with FCV), and correct PEEP and tidal volume settings (with conventional ventilation), see: Section 9. 'Study Procedures';
- correct FiO_2 settings, and respiratory monitoring (with both modes), see: Section 9. 'Study Procedures';
- significant deviation from the predefined standard ventilator settings (with both modes), PEEP and driving pressure titrations (with FCV) and PEEP and tidal volume (VCV) beyond preapproved deviations for safety, see: Section 9. 'Study Procedures'; and
- any significant deviation from the predefined settings based on surgeon's assessment of surgical conditions (rating influence of mechanical ventilation on: overall surgical conditions; visibility within the surgical field; motion artifact caused by mechanical ventilation, rated on a 7–point Likert scale ('very poor' to 'excellent').

*At least 80% of patients must receive ventilation exactly according to the study protocol. If compliance falls below 80% but remains above 40%, a traffic light system will guide progression: >80% (green) indicates that the trial can proceed as planned, 40-80% (amber) suggests that modifications are needed before advancing to a larger trial, and <40% (red) signals that the trial should be discontinued. Any deviation from the prescribed ventilator settings will be documented with detailed explanations to identify challenges encountered during the pilot trial.

Secondary Outcome

Secondary outcomes of this *pilot* are related to safety of the ventilation protocols, feasibility of the study protocol, and the effect of FCV on the incidence of PPCs, all meant to advance and confirm safety and feasibility of the ventilation strategies, and the suitability of the study protocol before proceeding with the main study.

Safety outcomes include:

- the need for rescue ventilation strategies, as a result from any significant deviations from the predefined ranges of the following parameters:
    - unacceptable intraoperative measures of gas exchange (measures outside the specified ranges defined as hourly PaO_2, and $PaCO_2$ measurements, and continuous SpO_2 and end–tidal CO_2 readings, see: Section 9. 'Study Procedures');
    - unacceptable low minute ventilation (outside the specified ranges for total minute volume, see: Section 9. 'Study Procedures');
    - unacceptable ventilator settings and ventilation parameters (outside the specified ranges defined as (hourly) tidal volume, respiratory rate, PEEP and PIP, FiO_2, driving pressure and mechanical power of ventilation, and respiratory system compliance and elastance);
- intraoperative respiratory complications, which are defined as (any time point) severe atelectasis and pneumothorax;
- intraoperative hemodynamic complications, which are defined as (any time point) occurrence of hypotension, defined as a mean arterial pressure (MAP) below 65 mm Hg, lasting > 1 minute (not related to the surgical course or anesthetic interventions, according to the attending anesthesiologist); *and* (hourly) vasopressor support (at the tolerance limit of the attending anesthesiologist) and dose; *and* (any time point) occurrence of arrhythmias, and intervention for arrhythmias.

Study protocol feasibility outcomes include:

- proper handling of the regulatory aspects of the study, including correct enrollment of patients (see: Section 8. ‘Study Population’) and correct randomization (see: Section 12. ‘Regulatory Aspects and Safety’);
- adherence to the study protocol, including, relevant ventilation strategy-related aspects; and relevant aspects not related to ventilation (see: Section 9. ‘Study Procedures’); and
- correct and complete collection of intraoperative and postoperative variables and outcomes.

The exploratory secondary outcome is defined as the effect of FCV on the incidence of PPC[16] on the non–surgical (i.e., ventilated) side, which includes:

- Dyspnea: new dyspnea, not because of other documented cause
- Bronchospasm (wheeze): newly detected or patient reported expiratory wheeze
- Upper airway obstruction: upper airway obstruction requiring treatment by a nasal airway, oral airway, or initiation of CPAP
- Tracheobronchitis: tracheal secretions increased in amount or changed in colour or purulence, associated with a normal radiological imaging or other imaging technique
- Atelectasis: radiological imaging or other imaging technique (e.g. by lung ultrasound) demonstrating lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
- Pleural effusion: radiological imaging or other imaging technique (e.g. by lung ultrasound) demonstrating blunting of the costophrenic angle, loss of 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
- Pulmonary congestion: clinical signs of congestion, including dyspnea, edema, rales, and jugular venous distention, with or without radiological imaging or other imaging technique (e.g. by lung ultrasound) demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates
- Suspected respiratory infection: an otherwise unexplained white cell count > 11.2 cells/mm^3 or administration of respiratory antibiotics postoperatively; positive signs of infection on sputum microbiology; production of purulent (yellow or green) sputum that was different from preoperative status
- Pneumonia: new or progressive radiographic infiltrates plus at least two of the following: antibiotic treatment, tympanic temperature > 38 °C, leukocytosis or leukopenia [white blood cell count < 4000 cells/mm^3 or > 12,000 cells/mm^3], and/or purulent secretions
- Aspiration Pneumonitis: evidence on radiological imaging or other imaging technique of acute lung injury with a clinical history consistent with inhalation of gastric contents
- Hypoxemic Respiratory failure (mild/moderate/severe)
- Hypercapnic respiratory failure: New onset or worsening previous hypercapnic respiratory failure needing treatment (e.g. (non-) invasive respiratory support)
- ARDS: as per the current global definition[23]
- Empyema
- Hemothorax
- Pneumothorax: diagnosis of a pneumothorax on radiological imaging or other imaging technique (e.g. lung ultrasound)
- Pulmonary embolism: diagnosed by radiological imaging or other imaging techniques and treated
- Bronchopleural fistula: Bronchopleural fistula with prolonged air leak
- Unplanned use of mechanical ventilation: unplanned prolonged mechanical (non-invasive or invasive) ventilation, requiring treatment, such as naloxone or increased use of manual or mechanical ventilation
- Reintubation: respiratory failure requiring endotracheal and mechanical or assisted ventilation
- Bronchoscopy: unplanned bronchoscopy not explained by surgical indication (e.g. for airway toilet)
- Surgical re-intervention: pulmonary complication needing surgical intervention

7. STUDY DESIGN

Rationale and justification of conducting a pilot trial

Small animal and human studies have demonstrated the promising respiratory benefits of FCV in various surgical and experimental conditions. In a single-center study in thoracic surgery with OLV, FCV demonstrated favorable results in terms of oxygenation and ventilation during the OLV phase. However, before a larger randomized clinical trial can be conducted to evaluate its effectiveness in improving patient outcomes, additional research is required. Specifically, studies need to focus on assessing the feasibility (regarding the comparability of the application of the ventilation strategy, setting of ventilation parameters, and adherence to the SOPs) and safety (regarding the effects of mechanical ventilation on vital parameters, hemodynamics, and respiratory complications, compared to events/values that are expected during conventional ventilation) of FCV during all phases of intraoperative ventilation, and in particular OLV in patients undergoing thoracic surgery. By ensuring its feasibility and safety in these contexts, future trials can more accurately determine its broader impact on patient care and clinical outcomes.

This international multicenter randomized clinical *pilot* trial will be conducted to test the feasibility and safety of FCV across all phases of intraoperative ventilation, in particular OLV, and its findings will be used to inform the design of a future trial testing efficacy with regard to PPCs.

Study design and justification of design

The *pilot* trial design will be prospective, randomized and controlled. All patients complying with our inclusion criteria and in the absence of any exclusion criteria will be included. Patients will be informed about the study sequence during preoperative anesthesia consultation to give their informed consent. Patients` data will be subsequently entered in the eCRF. Each participant will be linked with a unique identification code, which will be used for continuing process ("*Patient ID*"). Furthermore, baseline information (sex, year of birth, height, weight, BMI, date of surgery, indication of surgery, ASA score, medical history and allergies) will be recorded. Patients denying informed consent will be excluded from the pool of selected patients.

The intervention to be studied will either be the intraoperative FCV or VCV in thoracic surgery. Patients, randomly assigned to one study group, will be surveyed for the duration of hospitalization (until the 7th postoperative day or until discharge). Events complying with the respective outcomes and reporting of serious adverse events (SAE) are monitored.

Study duration

Duration of the whole study is expected to be 18 months. Recruitment is expected to finish after 12 months. The duration for a single participant will be approximately seven to 12 days (as defined as the duration to collect the exploratory secondary outcomes: PPCs).

Patient and public involvement

The exploratory secondary outcome, PPC, incorporated a "patient and public" concept. Patients or their representatives participated in the panel and were involved in the Delphi process to define PPC.[16]

Methods for minimizing bias

Allocation Bias: To minimize or avoid this type of bias, patients are blinded to their randomization after providing written consent. Blinding during the application of the respective interventions is not possible in this study due to the use of different ventilation devices (see below).
Selection Bias: To minimize selection bias, all patients will be assessed for eligibility automatically in the preoperative anesthetic clinic and we will attempt to recruit all eligible patients.

Randomization

Patients selected to participate will be randomized after giving their informed consent using a block randomization process. Randomization will be stratified by each center. Patients will be randomized 1:1 to either the FCV or the VCV group. Randomization will be conducted electronically, when participants` data will be entered in the eCRF.

Blinding procedures

Study participants are blinded to their group-specific intervention assignment after randomization, meaning that all patients will remain unaware of their allocation until the conclusion of the pilot study.
The treating physicians and the staff responsible for intra- and postoperative patient care cannot be blinded due to the use of different ventilation devices during the interventions. The same study personnel also conduct the postoperative follow-up assessments. Therefore, the study is conducted in a single blinded design.

Unblinding Procedures (Code break)

Unblinding procedures are not applicable as the patient is solely blinded to the intervention assignment.

8. STUDY POPULATION

Patients (n=140) scheduled for thoracic surgery with OLV will be enrolled. Patients will be included in selected centers in Switzerland, Germany, France, the Netherlands and Austria.

Eligibility criteria

Inclusion criteria:

- aged ≥ 18 years;
- scheduled for elective open, video– or robot–assisted thoracic surgery with OLV using a DLT; and
- able to give written informed consent to participate in the study and agree to comply with the study protocol prior to initiation of any study–mandated procedure and study intervention.

Exclusion criteria

- body weight < 40 kg;
- ASA Physical Status Classification System score IV – VI;
- lung separation with other method than DLT (e.g. difficult airway, tracheostomy);
- previous lung surgery;
- 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;
- documented pulmonary arterial hypertension > 25 mmHg mPAP at rest or > 40 mmHg syst. (estimated by ultrasound) or >20 mmHg mPAP measured by right heart catheterization, or pulmonary vascular resistance > 2.0 Wood units;[24]
- documented or suspected neuromuscular disease (thymoma, myasthenia, myopathies, muscular dystrophies, others);
- planned mechanical ventilation after surgery;
- bilateral procedures;
- surgery in prone position;
- persistent hemodynamic instability, intractable shock;
- intracranial injury or tumor;
- 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, pneumothorax, pulmonary embolism, purulent pleuritis, lung haemorrhage);
- documented preoperative hypercapnia > 45 mmHg (6 kPa)
- previous enrolment in the current study;
- being the study investigator of this study, his/her family members, employees and other dependent persons;
- if female and of childbearing potential, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating; or
- no written informed consent.

Note: female patients who are surgically sterilized/ hysterectomized or post-menopausal for longer than 2 years are not considered as being of child-bearing potential.

Note: in a recently conducted pilot trial on FCV (recruitment phase finished), the distribution of sexes with similar inclusion criteria, was comparable between groups.

Recruitment, screening and informed consent
The investigators will explain to each participant the nature of the *pilot* trial, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail with the possibility for the participant to ask questions. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorized individuals other than their treating physician.

All potential participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time will be given to the participant, in the setting of the preoperative anesthesia consultation to decide whether to participate or not. The process at least takes place, on the day before surgical procedures.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed and dated by the investigator, who explained the study, after the participant signed. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records. The informed consent process will be documented in the patient file and any discrepancy to the process described in the protocol will be explained.

All patients planned to undergo elective open, video– or robot–assisted thoracic surgery with OLV at participating centers will be informed of the potential to participate in the study during the preoperative anesthesia evaluation or during the participating center's screening process. Patients will be screened for eligibility using a checklist based on inclusion and exclusion criteria and previous medical history after written informed consent is given. Informed consent will be obtained in all patients prior to inclusion to the study and randomization process. For female participants of childbearing age, a pregnancy test (urine pregnancy test, and in case positive, confirmed by a serum pregnancy test) will be performed at screening visit. For participating centers, the regulatory requirements for excluding pregnancy will be aligned with the local regulations and the requirements of the respective local ethics committee at each center. Patients denying inclusion to the study will be documented as patients denying inclusion.

Inclusion of vulnerable participants is not intended in this study.

The investigator or the sponsor notifies the Ethics Committee of the first study participant, in accordance with art 62 lit. c ClinO, resp. art 38 ClinO. If the first participating person is not included in the trial within two years following the issuance of the authorization, the trial is considered interrupted (art. 23a ClinO). The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC as a substantial amendment.

Assignment to study groups
Patients given their informed consent will be randomly assigned 1:1 to either the ‘FCV’ or the ‘VCV’ group. Randomization will be conducted by using a block randomization process. To achieve a balanced distribution of groups per center, randomization will be stratified by center.

Criteria for withdrawal / discontinuation of participants
The criteria for withdrawal of participants are the request of participants to be withdrawn from the study; any serious adverse event plausibly related to the ventilation strategy; excess rescue crossover beyond a preset threshold and; severe hypoxemia/hypercapnia episodes exceeding predefined limits. In this

case, the patient is excluded from all ongoing study procedures. Information and data obtained before exclusion will be evaluated in regard of the outcome parameters. Missing intra– and postoperative data will be omitted from analyses.

9. STUDY PROCEDURES

The intervention to be investigated is an intraoperative ventilation strategy with individualized FCV with dynamic compliance guided titration of PEEP and driving pressure during all phases of intraoperative ventilation, and in particular OLV, aiming at maximum recruitment of lung tissue without causing overdistention. The intervention is compared to an intraoperative ventilation strategy with current best practice lung protective VCV with standard PEEP. Detailed information on the two ventilation strategies is provided thereafter. The study duration for an individual participant will be approximately seven to 12 days (as defined as the recruitment phase and the duration of PPC assessments).[16]

General anesthesiology procedures

Randomized assignment to the study groups will be conducted after inclusion of the patient. The individual assignment will be known to the attending anesthesiologist to prepare the respective ventilator. After induction of general anesthesia (which will follow the SOPs of the respective centers), intubation and ventilation with a DLT and conventional ventilator will be maintained until steady state parameters (SpO_2 >92%, correct placement of the DLT) have been achieved. Routine general anesthesia is performed according to the specific expertise and routine clinical use of each center. General anesthesia will be induced and maintained by using total intravenous anesthesia (TIVA) in both groups. TIVA, the standard of care for thoracic surgeries in most European countries, also ensures comparability. Quantitative neuromuscular monitoring (e.g., train–of–four (TOF) monitoring) is required. Before extubation, residual antagonization should be addressed (e.g., TOF >0.9).

Comparison of the intraoperative ventilation protocol

	Intervention TLV	Intervention OLV	Control TLV	Control OLV
Ventilator	EVONE	EVONE	standard operating room ventilator	Standard operating room ventilator
Mode	FCV	FCV	VCV	VCV
V_T	–	–	7 to 9 ml/kg PBW	5 to 6 ml/kg PBW
RR	–	–	target $etCO_2$ 4.5 to 5.8 kPa	target $etCO_2$ 4.5 to 5.8 kPa
Flow	target $etCO_2$ 4.5 to 5.8 kPa	target $etCO_2$ 4.5 to 5.8 kPa	–	–
I:E ratio	1:1	1:1	1:1 to 1:2	1:1 to 1:2
ΔP	compliance–guided titration	compliance–guided titration	target V_T 7 to 9 ml/kg PBW	target V_T 5 to 6 ml/kg PBW
PEEP	compliance–guided titration	compliance–guided titration	according to local practice	according to local practice
FiO2	SpO2 >92%	SpO2 >92%	SpO2 >92%	SpO2 >92%
Rescue (Desaturation SpO_2 < 92%)	increase FiO_2		increase FiO_2 + RM	
Further issues	1. according to FCV SOP; 2. switch to standard ventilator		1. according to VCV SOP	

FiO_2 SpO_2 > 92%

$etCO_2$ target $etCO_2$ 4.5 to 5.8 kPa

MAP 65mmHg

Anesthesia TIVA

Neuro Monitoring EEG guided

NMT TOF = 0; (extubation TOF > 0.9)

Detailed description of the intervention: FCV

In the FCV group, intraoperative ventilation will be provided with the EVONE (IES Ventinova Medical, Bizkaia Science and Technology Park Ibaizabal Bidea, 500, 1st floor 48160 Derio, (Bizkaia) SPAIN). PEEP and Ppeak are titrated guided by dynamic compliance, as follows: Starting from a default setting of 5 cmH_2O of PEEP and 15 cmH_2O of Ppeak, PEEP and Ppeak are equally increased by 1 cmH_2O steps and the PEEP value with the highest VT and thus highest dynamic compliance is defined as "best" PEEP. Subsequently, Ppeak is stepwise (+1 cmH_2O) increased until there is no further over-proportional increase in tidal volume (V_T) (i.e. measured V_T > expected V_T according to measured dynamic compliance), defined as best driving pressure. No recruitment maneuvers are carried out during FCV. With the I:E ratio set to 1:1, flow is adjusted to establish normocapnia (target etCO2 4.5 to 5.8 kPa). FiO_2 is adjusted to maintain oxygen saturation (SpO_2) >92%. It is left to the discretion of the attending anesthesiologist to use a higher fraction of FiO_2.

Rescue to VCV allowed in the following scenarios: technical malfunction of the ventilator conducting FCV, unexpected ventilation problems resulting in compromised oxygenation, ventilation, or CO_2 elimination, which cannot be resolved by adjusting the aforementioned parameters, based on the decision of the attending anesthesiologist.

Detailed description of the control intervention: VCV

In the VCV group, intraoperative ventilation will be provided by a standard anesthesia ventilator in use in the respective participating centers. Patients will be ventilated in VCV mode, at the lowest inspired FiO_2, to maintain SpO_2 > 92%. It is left to the discretion of the attending anesthesiologist to use a higher fraction of FiO_2. Inspiratory to expiratory ratio is set at 1:1 to 1:2, respiratory rate will be adjusted to target normocapnia (target $etCO_2$ 4.5 to 5.8 kPa. V_T will be set at 7 to 9 ml/kg predicted body weight (PBW) during TLV and 5 to 6 ml/kg PBW during OLV. The PBW is calculated according to a predefined formula: 50 + 0.91 x (centimeters of height – 152.4) for males and 45.5 + 0.91 x (centimeters of height – 152.4) for females.

Ventilation will start with a PEEP of 5 cm H_2O. Further adjustments, including increases or decreases during TLV and OLV, may be made at the discretion of the attending anesthesiologist.

Rescue to FCV mode is not allowed. Rescue to another conventional mode is allowed in the following scenarios: technical malfunction of the ventilator, unexpected ventilation problems resulting in compromised oxygenation, ventilation, or CO_2 elimination, which cannot be resolved by adjusting the aforementioned parameters, based on the decision of the attending anesthesiologist.

The ventilation strategy in the control group is designed as a pragmatic approach reflecting routine clinical practice across the participating centers. As this pilot trial primarily aims to assess feasibility, safety, protocol adherence, and implementation of the intervention rather than to compare efficacy regarding patient–centered outcomes, individualization of ventilatory parameters was intentionally avoided. In particular, PEEP management is left to the discretion of the attending anesthesiologist, as there is currently no conclusive evidence that individualized or high–PEEP strategies improve postoperative outcomes in this patient population, while several studies have reported an increased risk of hemodynamic impairment associated with higher PEEP levels or individualization strategies. Therefore, the selected ventilation approach can be considered representative of current standard care and appropriate for the objectives of this feasibility trial.

Thoracic insufflation

Thoracic insufflation, as part of a video– or robot–assisted procedure, is performed by the attending surgeon or anesthesiologist. The level of applied intra–thoracic pressure is suggested to be between 8 to 15 cm H_2O, but can be changed for clinical reasons as judged by the attending surgeon or anesthesiologist. The level of pressure applied will be documented in the eCRF. If no CO_2 (but other agents) will be used during thoracic insufflation, this will be documented in the eCRF.

Postoperative management

Postoperative pain management, physiotherapeutic procedures and fluid management will be performed in the intra–operative and/or post–operative period according to the specific expertise and routine clinical use of each center. The investigators suggest to adhere to the enhanced recovery after surgery (ERAS) guidelines (http://erassociety.org/guidelines/list-of-guidelines/): [25]

- to perform postoperative pain management in order to achieve a VAS/NRS pain score below
- 4, and regional or neuraxial analgesia can be used whenever indicated;
- 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 overload (according to the discretion of the attending anesthesiologist); and
- to use appropriate prophylactic antibiotics when indicated

Furthermore, regarding surgical perioperative procedures, the investigators suggest adhering to the Safe Surgery Checklist from the World Health Organization (Safe surgery [www.who.int]).

Data collection and follow-up for withdrawn participants

Patients who withdraw early from the study and no longer participate in the intervention will be excluded from the further course of the trial. The parameters collected up to the point of withdrawal from the study will still be pseudo-anonymized and used for the analysis of the respective endpoints. All data collected will be stored in the eCRF.[26] Non-electronic data will be stored in the study administration office, which will be just accessible to the study personal. Continuous parameters (as perioperative vital parameters, and ventilation parameters) obtained during mechanical ventilation will be documented in the (electronic) anesthesia protocol and stored behind the institution`s firewall.

Specific preventive measures

Apart from the study intervention, preoperative assessment, anesthesia procedures and postoperative pain management will be provided according to written institutional SOP of the respective center. Equipment and medication for resuscitation and treatment of adverse events occurring during and after anesthetic procedures are available in all operation theatres, the PACU and ICU according to institutional SOP of the respective center. In addition, trained personal is permanently available in all locations. All information on intraoperative medication and hemodynamic parameters is stored in an electronic database or anesthesia protocol according to institutional SOP of the respective center. Any deviations resulting in clinically relevant consequences will be treated immediately by the attending physician. Any SAE or safety outcomes related to the perioperative ventilation strategy will be documented and treated according to written institutional SOP of the respective center and all procedures will adhere to the measures and reporting deadlines required by the regulatory authorities.

Rescue measures

In case of ventilation problems (impaired ventilation, oxygenation, or decarboxylation), the following rescue maneuvers, based on the decision of the attending anesthesiologist, may be considered depending on group assignment:

- Impaired ventilation: If not due to tube dislocations, obstructions or airway problems, a switch from FCV ventilation to VCV may be considered. Recruitment maneuvers are possible during VCV, based on the decision of the attending anesthesiologist;
- Impaired elimination of CO_2: if not due to emphysema during thoracic insufflation or airway problems: in the FCV group, flow can be increased stepwise (+1 L/min) to increase minute volume; in the VCV group minute volume can be increased by increasing tidal volume or respiratory frequency, based on the decision of the attending anesthesiologist; and
- Impaired oxygenation/desaturation (defined as $SpO_2 \leq 90\%$; or if preoperative $SpO_2 < 90\%$, an absolute decrease in $SpO_2 > 5\%$) in patients could indicate the presence of overdistention of aerated lung tissue or atelectasis. If desaturations occur, in the absence of airway problems, severe hemodynamic impairment, or ventilator malfunction, a rescue strategy is allowed in which recruitment maneuvers, increase or decrease of PEEP (above or below 5 cm H_2O), oxygen insufflation to the non–dependent lung, CPAP to the non-dependent lung, TLV to improve

oxygenation are performed or the FiO_2 is increased, based on the decision of the attending anesthesiologist.

- Impaired hemodynamics: PEEP during OLV can also be lowered (rescue) for hemodynamic problems

Preapproved protocol deviations

In both groups, the attending anesthesiologist is allowed to change ventilator settings at any time point upon the surgeons' request or if there is any concern about patient's safety. If one of the following complications occurs and does not respond to conventional therapy, ventilation mode can be changed, according to the judgement of the anesthesiologist in charge:

- after PEEP titration, a mean arterial pressure < 65 mmHg, lasting longer than one minute, not responding to fluids and/or vasoactive drugs;
- new arrhythmias not responding to the treatment suggested by the Advanced Cardiac Vascular Life Support Guidelines;[27]
- need for a dosage of vasoactive drugs at the highest level tolerated, according to the decision of the anesthesiologist in charge;
- need of massive transfusion, more than 5 units of blood to maintain hematocrit > 21% and hemoglobin > 7 mg/dl; and
- surgical complication resulting in life–threatening situations.

10. STUDY ASSESSMENTS

Assessments of Outcomes

Preoperative Assessments

To determine preoperative baseline parameters, the following data will be documented in the eCRF:

- eligibility and inclusion/exclusion criteria during the preoperative anesthesia consultation; and
- baseline parameters (age, gender, weight/height/BMI, ASA–Score, type of surgery, pulmonary disease (COPD), smoking status, baseline oxygenation (SpO_2)).

Assessment of Primary Outcome

To evaluate the feasibility issues of the ventilation protocols, the following data will be documented in the eCRF:

- implementation and adherence of the assigned ventilation strategy (with both modes) during all phases of intraoperative ventilation, as described in the respective ventilation protocol;
- predefined standard ventilator settings (with both modes);
- implementation of the correct titration of PEEP and driving pressure (with FCV), and correct PEEP and tidal volume settings (with conventional ventilation);
- evaluation of correct FiO_2 settings, and respiratory monitoring (with both modes);
- evaluation of significant deviations from the predefined standard ventilator settings (with both modes), PEEP and driving pressure titrations (with FCV) and PEEP and tidal volume (VCV) beyond pre–approved deviations for safety; and
- evaluation of any significant deviation from the predefined settings based on surgeon's assessment of surgical conditions (rating of: overall surgical conditions; visibility within the surgical field; motion artifact caused by mechanical ventilation).

Assessment of Secondary Outcomes

To evaluate the safety of the ventilation protocols, feasibility of the study protocol, and the effect of FCV on the incidence of PPCs, the following data will be documented in the eCRF:

Safety:

- gas exchange: (hourly) PaO_2 and $PaCO_2$, and SpO_2 and end–tidal CO_2;
- minute ventilation: (hourly) total minute volume;
- ventilator settings and ventilation parameters: (hourly) tidal volume, respiratory rate, PEEP and, FiO_2, Ppeak, driving pressure and mechanical power of ventilation, and respiratory system compliance;
- intraoperative respiratory complications;
- (any time point) pneumothorax or severe atelectasis;
- intraoperative hemodynamic complications, which are defined as (any time point) occurrence of hypotension, defined as a mean arterial pressure (MAP) below 65 mm Hg, lasting longer than 1 minute (not related to the surgical course or anesthetic interventions, according to the attending anesthesiologist);
- surgical settings (hourly) including patient positioning, thoracic insufflation (agent and pressures), decubitus position;
- influence of mechanical ventilation on: overall surgical conditions; visibility within the surgical field; motion artifact caused by mechanical ventilation, rated on a 7–point Likert scale ('very poor' to 'excellent') assessed by the surgeon;
- (hourly) vasopressor support and dose; and
- (any time point) occurrence of arrhythmias.

Study protocol feasibility:

- evaluation of the handling of the regulatory aspects of the study, including correct enrollment of patients; and
- evaluation of adherence to the study protocol, including, relevant ventilation strategy–related aspects; and relevant aspects not related to ventilation.

Assessment of Explorative Secondary Outcomes
To determine the incidence of the PPCs within the first seven postoperative days documented PPCs as defined in the study outcomes will be documented in the eCRF.

Assessments in participants who prematurely stop the study
Patients who wish to terminate their participation in the study prematurely will be visited during the regular postoperative anesthesia assessments. The parameters collected up to the point of withdrawal from the study will be evaluated.

Follow–up of the participants after the regular termination of the study
The follow–up of the study will be until the 7th postoperative day or until the patient leaves the hospital, whatever comes first. Regular postoperative anesthesia visits will take place in addition to the collection of endpoint parameters.

Study Visit Plan

	Enrolment	Random-ization									
Place			OR						PACU /ICU	ICU /ward	
General Timepoints	preoperative (day -7 to -1)		POD0 (day 0)							POD 1-7 (day 1-7)	discharge
Perioperative Timepoints			T-1	T0	T+0.5	T+1	T+… (each hour until end of surgery)	Tx extubation	Ty postop		
Enrolment											
IC (before eligibility)	+										
Eligibility	+										
Randomization		+									
Baseline & Scores											
Sex, Age, height, weight, BMI, Smoker, pulmonary disease	+										
ASA Score	+										
Intervention											
FCV				+	+	+	+				
VCV				+	+	+	+				
Primary Outcome											
Feasibility	+	+	+	+	+	+	+				
Surgical conditions (7-point Likert)									+		

Secondary Outcomes											
Safety			+	+	+	+	+				
Feasibility of the protocol				+	+	+	+	+	+	+	
Completeness of eCRF										+	+
PPCs								+	+	+	+
Safety											
AE/SAE			+	+	+	+	+	+	+	+	+

POD postoperative day; T-1 TLV start, after induction; T0 initiation of OLV; T+0.5 30 min of OLV; T+1(…) hourly OLV; Tr post-re-expansion in TLV; Tx post-extubation; Ty PACU/ICU arrival

11. STATISTICS AND METHODOLOGY

Hypothesis

FCV is a feasible and safe OLV strategy in patients undergoing (open, video– or robot–assisted) thoracic surgery.

Determination of Sample Size

To estimate the appropriate sample size for this *pilot* trial, we considered both feasibility and safety across multiple centers. Assuming a target of 10 participants per randomization group in each of the centers, the total sample size is 140 participants (7 centers × 10 participants × 2 randomization groups). This number balances logistical feasibility, i.e., currently approx. 2–3 eligible cases at HOCH Health Ostschweiz per week, with the need for adequate data to assess safety outcomes.

This *pilot* trial primarily aims to assess the feasibility of the FCV strategy in patients scheduled for thoracic surgery. Additionally, it will assess the safety and the incidence of PPCs in this *pilot* trial, which can be used to inform the design of a future trial testing its efficacy with respect to postoperative outcomes. The *pilot* trial is not powered to detect any impact on clinical outcomes.

The rationale of this number is based on previous (and ongoing) pilot studies of FCV (i.e., PROFLOW–ROBOTic pilot; NCT06703814 and HumRes66140) and balances logistical feasibility with the need for adequate data to assess safety outcomes.

Statistical criteria for termination of the study

Not applicable.

Planned Analyses

All statistical analyses for the trial will be conducted according to the intention–to–treat principle. Descriptive analyses will be conducted, focusing on the progression outcomes of the study. Given the exploratory nature of this pilot study, we will present mean differences alongside 95% confidence intervals to highlight potential trends in compliance with the ventilation strategies and data variability.

A comprehensive statistical analysis plan will be published online on ClinicalTrials.gov before database is cleaned and closed.

Interim analyses

With the certification of the ventilator and the adherence to the manufacturer's guidelines for using the ventilation mode, there are no indications of compromised safety for patients receiving FCV ventilation. As a result, an interim analysis is deemed unnecessary and can be omitted confidently.

Handling of missing data and drop–outs

Missing perioperative data and laboratory data will be omitted from analyses. PPCs will be assessed daily during hospitalization until discharge or the 7th postoperative day, whichever occurs first. Participants discharged before the 7th postoperative day complete the study at discharge; no post–discharge assessment will be performed. Early discharge is not considered missing outcome data. Missing outcome data may occur due to withdrawal of consent, transfer without record access, or incomplete documentation. Missing data will be handled as “data unknown” rather than “no PPC”. A drop–out rate >10% (i.e., >10 participants) will be covered by additional recruitment in the respective center.

12. REGULATORY ASPECTS AND SAFETY

Local regulations / Declaration of Helsinki
This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH–GCP applied mutatis mutandis according to the Ordinance on Clinical Trials in Human Research, the HRA as well as other locally relevant legal and regulatory requirements.

(Serious) Adverse Events and notification of safety / protective measures
An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a study intervention, which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence for which it cannot be excluded that the event is attributable to the intervention under investigation and that

- requires in–patient hospitalization not envisaged in the protocol or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity
- is life–threatening or results in death, or
- causes a congenital anomaly or birth defect.

In this study, hospitalization is defined as an overnight stay in a hospital unit and/or emergency room due to an AE. An additional overnight stay defines a prolongation of existing hospitalization. The following is not considered a SAE: Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

Life–threatening refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.

Health hazards that require measures
Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants.

Assessment of Causality
Both the Sponsor (i.e., Dr. Timur Yurttas, HOCH Health Ostschweiz, Switzerland) and the Investigator of the respective site make a causality assessment to the study intervention of safety events, based on the criteria listed below.

Categories to determine the relationship to the study intervention

Relationship	Description
Not related	The event is definitely not associated with application of study intervention; a relationship can be ruled out.
Related	The relationship between application of study intervention and the event is possible, but other causes cannot definitely be ruled out or the event is definitely associated with application of study intervention.

Assessment of Intensity
The intensity of events will be graded by the Investigator of the respective site according to a three–point scale as provided in the table below: mild, moderate, and severe and reported on the safety forms in the eCRF. The highest grade observed within a period will be recorded. Events that are graded as mild, moderate or severe may or may not be serious. These terms are only used to describe the intensity

of a specific event, while seriousness rather than intensity serves as a guide for defining regulatory reporting obligations.

Three–point scale to assess intensity of adverse events

Grade	Definition
Mild	Event may be noticeable to participant, does not influence treatment, usually does not require intervention
Moderate	Event may cause discomfort that interferes with usual activities or be dangerous for the participant; intervention may be needed.
Severe	Event may cause noticeable disability; participant may not be able to continue in the study; treatment or intervention is usually needed.

Assessment of Seriousness

Both the Sponsor and the Investigator of the respective site will assess seriousness of safety events based on the definition listed above. The Investigator will document the events in line with the clinical study protocol. The Sponsor will document the assessment in the trial documentation.

Assessment of Expectedness

The Sponsor assesses expectedness of safety events based on the criteria listed below:

Criteria to determine the expectedness

Category	Description
expected	The event is definitely expected with application of study or control intervention and be described as such in the instructions for use.
unexpected	The event is not expected with application of study or control intervention and not be described as such in the instructions for use.

Reporting of SAEs (see ClinO, Art. 63)

All intervention–related SAEs are documented and reported immediately (within a maximum of 24 hours after the site becoming aware of the SAE) to the Sponsor of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation (i.e., the SAE is definitely, probably, or possibly related to the intervention), the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Both ventilation strategies (FCV & VCV) used during the study phase have been approved for several years, the medical devices performing these ventilation techniques are CE certified and are operated in accordance with the manufacturer's instructions during the study. Accordingly, we do not gain any additional value for our study objective by documenting all AEs that may occur during the perioperative or postoperative course. The surgical procedure in particular bears the possibility of the occurrence of e.g. postoperative abnormal laboratory parameters. Any abnormal parameter or clinical event is investigated in accordance with the SOP of the respective department/treating physicians, but is not documented as AE or reported to the Sponsor unless it is an intervention–related event, which is defined as intervention–related SAE.

Thus, the documentation of adverse events is restricted to intervention–related SAEs. Ventilation–related complications that meet the definition of intervention–related SAEs will be documented SAE.

Nevertheless, throughout the entire study phase, we will ensure patient safety and treat any events that could have an impact on the health of patients and study participants in accordance with our in-house protocols.

All intervention-related SAE will be collected from the time of study intervention start until postoperative day 7 or discharge, which may occur earlier. During the screening period, no SAEs will be documented.

Follow up of (Serious) Adverse Events
All intervention-related **SAE** are collected, fully investigated and documented in the source document and appropriate CRF during the defined period for safety data collection.

Documentation of intervention–related SAEs by the investigator of the respective site includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, co–medication and concomitant diseases, assessment of intensity, seriousness and causal relationship to the study intervention.

Events complying with the definition of intervention–related SAE will be collected during the whole course of the trial and will be documented in the eCRF accordingly.

If an event occurs that meets the criteria of the intervention–related SAE the patient is treated according to the internal standards. In this case, the follow–up by the study team includes the period until the end of the study or the end of the event defined as intervention–related SAE.

Reporting and Handling of Pregnancies
Pregnant women are not allowed to be enrolled into this study. Due to the short duration of the patient being exposed to the study intervention and as no pharmacological treatment is involved and as pregnant women are excluded from the trial, any pregnancy occurring in a study patient after study intervention must not be reported.

Notification of safety and protective measures (see ClinO, Art 62, b)
If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

Periodic reporting of safety and general progress of the clinical trial
Once a year, the investigator submits to the Ethics Committee a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43). The safety report and the general study progress report contain information from all sites including information from sites outside of Switzerland. The Sponsor distributes the reports to all the participating Investigators.

Amendments
Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well–being of human participants may proceed without prior approval of the Ethics Committee. Such deviations will be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of coordinator/principal-investigator and sponsor (ClinO, Art. 29).

A list of all non–substantial amendments will be submitted once a year to the competent EC together with the safety/general study progress report.

Notification and reporting upon completion, discontinuation or interruption and resumption of the study.

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38).

The Sponsor may terminate the study prematurely according to certain circumstances, e.g. because of

- ethical concerns;
- insufficient participant recruitment:
- when the safety of the participants is doubtful or at risk (e.g. when the benefit–risk assessment is no longer positive);
- alterations in accepted clinical practice that make the continuation of the study unwise; or
- early evidence of harm or benefit of the experimental intervention.

Upon premature study termination or study interruption or resumption (including reasons thereof), the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38). An interruption lasting more than two years is considered a premature termination.

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

Insurance

In the event of study–related damage or injuries, the liability of the Sponsor for the trial provides compensation, except for claims that arise from misconduct or gross negligence, for this liability lies with respective participating centers. The insurance covers damage occurring up to 20 years after the end of the clinical trial.

13. FURTHER ASPECTS

Overall ethical considerations and risk benefit assessment

The aim of this *pilot* trial is to investigate the feasibility and safety of FVC in patients undergoing thoracic surgery, and to inform the design of a future trial testing its efficacy with regard to postoperative outcomes. Given that ventilation strategies inherently carry certain risks, yet remain essential in the context of general anesthesia and surgery, it is ethically justified to first conduct a pilot trial. The potential benefits of FCV are significant and warrant investigation. Based on the existing safety data from multiple clinical studies, FCV does not pose any significant additional risk compared to treatment in the control group. Participation in the study also does not entail any risks regarding the security of personal information or health data. These data are collected and stored in accordance with the required regulations and are accessible only to authorized study personnel (i.e., data encryption, restricted access to the database and study office, and the sponsor's internal firewall). Therefore, we find it appropriate to compare FCV with existing strategies such as VCV, as we anticipate meaningful improvements in patient outcomes with minimal additional risk. The participants in the study receive no compensation.

14. QUALITY CONTROL AND DATA PROTECTION

Data handling and record keeping / archiving
Data collected will be documented and stored in an electronic data system eCRF. All data collected will be treated in confidence and storage system will be validated and compliant to GCP.

Case Report Forms
The data collected for each research topic form the subject eCRF, which covers the following domains/topics:

- inclusion and exclusion criteria, and informed consent;
- information about planned surgery and methods of anesthesia;
- patient demographics;
- primary outcome parameters (feasibility);
- secondary outcome parameters (safety);
- other secondary outcome parameters (feasibility of protocol, database, PPCs, surgical conditions);
- serious adverse events (defined in section 10); and
- additional comments.

Perioperative vital parameters (continuous parameters, i.e.: blood pressure, heart rate, oxygen saturation, etc.) will be documented in the (electronic) anesthesia protocol. No participant–identifying information will be stored in the eCRF.

Specification of source data and source documents
Electronic sources of data include the electronic medical documentation systems (compliant to GCP). Paper source data include the informed consent, the inclusion/exclusion criteria form, and the perioperative ventilation parameter form.

Archiving of essential study documents
All the documents of the study will be archived for a minimum of 20 years after regular or premature termination of the study. Thereafter the data will be destroyed or deleted respectively.

Data management
All data collected will be stored in the eCRF on a password protected server (Castor EDC (Electronic Data Capture), provided by Castor)[26] (compliant to GCP) and administered by the data manager. Nonelectronic data will be stored in the respective study administration office.

Monitoring and Registration
Monitoring at the trial sites St. Gallen will be performed by the CTU St. Gallen according to a Monitoring Plan provided by the Clinical Trials Unit. Access to all source and study–specific documents will be granted to authorized monitoring personnel, and any related inquiries will be addressed by the study staff. The study will be registered in the Swiss Human Research Portal (HumRes) via BASEC in the national language of Switzerland in which recruitment is intended as well as on the platform ClinicalTrials.gov.

Confidentiality, Data Protection
The Sponsor/Principal–Investigator affirms and upholds the principle of the participants' right to privacy and shall comply with applicable privacy laws. Particularly the anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant confidentiality shall be protected by assigning each participant a unique numerical identifier to be used in lieu of their name in the study database. The Investigator confirms that they possess the required knowledge and expertise in data protection and will ensure the implementation of all necessary security measures. Data access will just be granted to authorized study staff. The participant identification list will be stored in the study administration office.

For data verification purposes, authorized representatives of the Sponsor (Investigator) or an ethics committee may require direct access to the medical records relevant to the study, including participants' medical history.

Storage of related health data

All data and exports of electronic records will be stored with access permissions/audit trail, fulfilling GCP and Swissethics requirements and stored on a secure database server.

General Points:

- no patient–identifying information is saved at any point; and
- only authorized study personnel have access to study data.

15. FUNDING, PUBLICATION AND DECLARATION OF INTEREST

Funding is guaranteed by departmental and institutional funds. We intend to seek further external noncommercial funding. We are primarily seeking financial support through the application for the institutional grant from the Research Committee of HOCH Health Ostschweiz, Cantonal Hospital St. Gallen. The main results of this study will be published in an international, peer–reviewed journal and if possible presented at scientific meetings. Sex and gender effects (any or none) will be published in the final study report. A summary of the results for the general public or the discontinuation of the study will be uploaded to BASEC within one year of the study's completion. An additional lay summary of the results or reasons for discontinuation will be published online in BASEC. Authorship in any publications will be granted in accordance with the International Committee of Medical Journal Editors (ICMJE) recommendations and follow the requirements of the PROVE Network and its transparency and publication policies.

More information for researchers can be found on the official PROVE Network website (https://www.provenetwork.org/information-for-investigators).[28]

This study protocol and the pseudonymized raw dataset will be published as well. The publication process shall be under the direction of the sponsor.

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