Official Study Title
PROtective Ventilation With FLOW–Controlled Ventilation to Improve Postoperative Pulmonary Outcome After ROBOT–Assisted Laparoscopic Surgery – an International Multicenter Pilot Randomized Clinical Trial.

Study Acronym: PROFLOW
ClinicalTrials.gov Identifier: NCT06703814
Document Version: 1.3
Document Date: 02 July 2025
Study Investigators: The PROFLOW–ROBOTic Investigators

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Clinical Study Protocol

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

SHORT TITLE: PROFLOW–ROBOTic *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 (NCT06703814) and the Swiss Human Research Portal (HumRes66140). 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:	Pressure–controlled ventilation
Study Identifier:	CTU 24/045 EKOS 24/197; BASEC No.: 2024-02197
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Study Short Title:	PROFLOW–ROBOTic *pilot*
Version and Date:	Version 1.3, 02.07.2025

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SPONSOR SIGNATURE PAGE(S)

Study identifier: CTU 24/045; EKOS 24/197

Study Title: PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after ROBOT–assisted laparoscopic surgery – an international multicenter *pilot* randomized clinical trial.

The Sponsor and the Statistician have approved the updated and finalized protocol Version 1.3, 02.07.2025, and confirm 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: Prof. Dr. Markus Lüdi, HOCH Health Ostschweiz, Cantonal Hospital St. Gallen, Switzerland



02.07.2025

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Statistician:
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02.07.2025

Date | Signature

LOCAL PRINCIPAL INVESTIGATOR AT STUDY SITE

Study identifier:	CTU 24/045; EKOS 24/197
Study Title:	PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after ROBOT–assisted laparoscopic surgery – an international multicenter pilot randomized clinical trial.
Protocol Version and Date:	Version 1.3, 02 July 2025

I confirm that I have read and understood this clinical study protocol and agree to conduct the trial as set out in this clinical study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH–GCP guidelines, and the local legally applicable requirements. I will abide by the publication plan set forth in my agreement with the Sponsor. I will promptly submit the protocol to applicable Competent Ethical Committee and will not begin the study until applicable approval has been obtained.

Name and address of Site

Printed name of Principal investigator

Date Signature

Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

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STUDY SYNOPSIS

Sponsor	Prof. Dr. Markus Lüdi Department of Anaesthesiology, Rescue- and Pain Medicine HOCH Health Ostschweiz, Cantonal Hospital St. Gallen Rorschacherstrasse 95, 9007 St. Gallen, Switzerland Phone: +41 71 494 15 01, E-Mail: markus.luedi@kssg.ch
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Title:	PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after ROBOT–assisted laparoscopic surgery – an international multicenter *pilot* randomized clinical trial.
Short title / Study ID:	PROFLOW–ROBOTic *pilot*
Protocol version and date:	Version 1.3, 28.04.2025
Registration:	The study is registered at clinicaltrials.gov (NCT06703814) and the Swiss Human Research Portal (HumRes66140). 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 pressure–controlled ventilation (PCV) in patients scheduled for robot–assisted laparoscopic abdominal, urologic, or gynecologic surgery. This *pilot* trial is designed to test the safety and feasibility of FCV, and to inform the design of a future trial testing the efficacy of FCV with regard to postoperative outcomes, including postoperative pulmonary complications. 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. With not 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:	The optimization of intraoperative ventilation is important in patients under general anesthesia, when physiologic breathing is replaced by non–physiologic artificial ventilation. Especially in patients undergoing robot–assisted laparoscopic surgery, intraoperative ventilation can be challenging, because of changes in compliance of the respiratory system and associated problems in gas exchange, due to the pneumoperitoneum and often extreme body positioning. Intraoperative lung–protection strategies have steadily improved in recent years to reduce complications from mechanical ventilation, but postoperative pulmonary complications remain a risk factor for increased morbidity and mortality. This *pilot* trial will be conducted to evaluate the safety and feasibility of intraoperative FCV during robot–assisted laparoscopic abdominal, urologic, or gynecologic surgery, and will inform the design of a future trial that will test the efficacy of intraoperative FCV compared to PCV in these patients.

Risk / Benefit Assessment	FCV has demonstrated beneficial physiologic effects in small–sized animal and human studies. Studies assessing its safety and feasibility, especially in patients undergoing robot–assisted laparoscopic abdominal, urologic, or gynecologic surgery are needed to help design a larger randomized clinical trial to assess its efficiency with respect to patient outcomes. The here proposed international multicenter randomized clinical *pilot* trial will be conducted to test the safety and feasibility of FCV, and its findings will be used to inform the design of a future trial testing the efficacy with regard to postoperative pulmonary complications.
Hypothesis	FCV is a safe and feasible ventilation strategy in patients undergoing robot–assisted laparoscopic surgery.
Objective(s):	The primary objective of this study is to evaluate the safety of intraoperative FCV in patients undergoing robot-assisted laparoscopic surgery, with a focus on: • gas exchange, including both oxygenation and decarboxylation; • minute ventilation, during all phases of intraoperative ventilation; • key ventilator settings and ventilation parameters; • respiratory complications, including pneumothorax *and* • hemodynamic complications, including hypotension and arrhythmias. The secondary objectives are to assess the feasibility of intraoperative FCV and the study protocol in patients undergoing robot-assisted laparoscopic surgery, including an evaluation of the use of FCV. • the need for rescue ventilation strategies, i.e., whether FCV (as well as PCV) can be used during all phases of intraoperative ventilation; *and* • compliance with the study protocol, omissions in the eCRF, and the feasibility of follow–up, i.e., how well each PPC can be captured. The explorative secondary objective concerns the primary endpoint of a future randomized clinical trial testing the efficacy of FCV, i.e., its effects on postoperative pulmonary complications. Herein we will determine the exact incidence, and define the effect size of the intervention.

Outcome(s) and Measurements Procedures:	The primary endpoint of this *pilot* trial is a set of safety parameters for FCV, including: • gas exchange: (hourly) PaO_2, $PaCO_2$, 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 PIP, FiO_2, driving pressure and mechanical power of ventilation, and respiratory system compliance and elastance; • intraoperative respiratory complications: (any time point) pneumothorax. • intraoperative hemodynamic complications: (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); *and* (hourly) vasopressor support and dose; *and* (any time point) occurrence of arrhythmias, and intervention for arrhythmias. Secondary endpoints focus on evaluating the feasibility of intraoperative FCV and the study protocol, including: • ventilation protocol adherence; *and* • study protocol adherence; *and* • completeness of the eCRF and follow-up of PPCs. The explorative secondary endpoint will compare FCV with PCV ventilation with respect to predefined and previously used postoperative (pulmonary) complications in the first seven postoperative days, including: • mild respiratory failure, defined as the occurrence of one or multiple of the following conditions after more than two days postoperatively: the occurrence of oxygen saturation (SpO_2) < 90% or partial pressure of oxygen in the arterial blood (PaO_2) < 7.9 kPa (or < 50 mm Hg) on room air, but responding to supplemental oxygen; *or* a sudden increase in supplemental oxygen requirement to maintain adequate saturation (SpO_2 > 90%) in patients receiving routine postoperative oxygen therapy; *or* any level of supplemental oxygen; • severe respiratory failure, defined as need for noninvasive or invasive mechanical ventilation, or a PaO_2 < 60 mm Hg (or < 7.9 kPa) or SpO_2 < 90% despite supplemental oxygen in spontaneously breathing patients; • dyspnea, defined as the patient`s perception of an uncomfortable abnormal awareness of breathing or respiratory limitation (shortness of breath, inability to take a deep breath, or chest tightness); • productive cough, defined as cough that produces sputum or mucus; • bronchospasm, defined as newly detected expiratory wheezing treated with bronchodilators; • suspected pulmonary infection, defined as receiving antibiotics and meeting at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest radiograph when clinically indicated, tympanic temperature > 38.3°C, white blood cell count > 12,000/µL; • pulmonary infiltrate, defined as any unilateral or bilateral infiltrates on chest radiography; • aspiration pneumonitis, defined as respiratory failure after the inhalation of regurgitated gastric contents;

	• atelectasis, defined as lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non–atelectatic lung on chest radiography; • ARDS (according to the new global definition of ARDS);[23]

	• pleural effusion, defined as blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows on chest radiography; • pneumothorax, defined as air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiography; • cardiopulmonary edema, defined as clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest radiograph demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates; *and* • death in hospital (defined as death from any cause during hospitalization).
Design:	International multicenter randomized clinical *pilot* trial.
Inclusion / exclusion criteria:	Inclusion criteria: • aged ≥ 18 years; *and* • scheduled for elective robot–assisted laparoscopic abdominal, urologic or gynecologic surgery in supine or Trendelenburg position; • **AND** with an increased risk of PPC, according to the ARISCAT risk score (≥ 26 points); • **OR** the combination of age > 40 years, scheduled surgery lasting > 2 hours and planned to receive an intra–arterial catheter for blood pressure monitoring during the surgery; *and* • able to give written informed consent. Exclusion criteria: • body weight < 40 kg; • ASA Physical Status Classification System score IV – VI; • previous enrolment in the current study; • being the study investigator of this study, his/her family members, employees and other dependent persons; • 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:	Pressure–controlled ventilation.
Number of subjects with rationale:	To estimate the appropriate sample size for this *pilot* trial, we considered both safety and feasibility across multiple centers. Assuming a target of 10 to 15 participants per randomization group in each of the four centers, the total sample size would range from 80 to 120 participants (4 centers × 10–15 participants × 2 randomization groups). For practical purposes and to ensure a robust assessment of the trial's objectives, we have selected a total sample size of 70 participants in Switzerland (with 30-60 patients being investigated in additional European centers in a separate, but identical study (due to regulatory aspects)). This number balances logistical feasibility with the need for adequate data to assess safety outcomes.
Duration of the study:	Four months from start of screening of patients.

Study schedule:	First-Patient-First-Visit: Q2 2025 (expected) Last-Patient-Last-Visit: Q3 2025 End-of-Trial: Q4 2025
Study Site:	Department of Anesthesiology, Rescue- and Pain Medicine, HOCH Health Ostschweiz, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; Department of Anesthesiology, Cantonal Hospital Luzern, Luzern, Switzerland; An identical study will be conducted independently at the Department of Anesthesiology, Amsterdam University Medical Centers, Amsterdam, The Netherlands. and the Department of Anesthesiology, Intensive Care and Pain Medicine, BG University Hospital Bergmannsheil, Ruhr-University Bochum, Bochum, Germany, under the same conditions for regulatory reasons, each enrolling 30 patients. The data will later be jointly analyzed as part of a research collaboration. The separate setting is required due to different operations for fulfilling the varied applicable clinical research laws in these countries.
Statistical considerations:	This *pilot* trial primarily aims to assess the safety of the FCV strategy in patients scheduled for robot–assisted laparoscopic abdominal, urologic, or gynecologic surgery, and evaluate its feasibility. Additionally, the incidence of postoperative pulmonary complications in this *pilot* trial 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 of clinical outcomes.
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) and Swissethics requirements and stored on a secure database server.
Ethical consideration	The aim of this *pilot* trial is to investigate the safety and feasibility of FVC 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. Therefore, we find it appropriate to compare FCV with existing strategies such as PCV, as we anticipate meaningful improvements in patient outcomes with minimal additional risk.
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.

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ANOVA	Analysis of Variance

ARISCAT	Assess Respiratory Risk in Surgical Patients in Catalonia
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
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
ISF	Investigator Site File
ITT	Intention to treat
OLV	One–lung ventilation
PACU	Post–anesthesia care unit
PCV	Pressure–controlled ventilation
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
TIV	Tidal impedance variation
VCV	Volume–controlled ventilation
VILI	Ventilator induced lung injury

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr., Version Date	**Chapter**	**Description of change**	**Reason for the change**
1.1, 07.11.2024	multiple	Clarifications in the sections background, study procedures, statistical analyses, quality measures, publications process	Adaptions according to reference EKOS 07.11.2024

1.2, 19.12.2024	Safety	Updated header and definition	Adaptions according to reference EKOS 19.12.2024
1.3, 28.04.2025	Multiple	Change of institutional affiliation and name. update participating centers, change of statistician, adapted sample size in Switzerland, change of randomization distribution per center, addition of references	New name of the leading hospital/sponsor site, additional changes due to updated management of the study procedures and regulatory aspects

1. STUDY ADMINISTRATIVE STRUCTURE

Sponsor

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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

Flow-controlled ventilation (FCV) differs from conventional ventilation modes in several key ways. Unlike pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV), FCV maintains a constant airflow during both the inspiration and expiration phases.[1] 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).[2] 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]

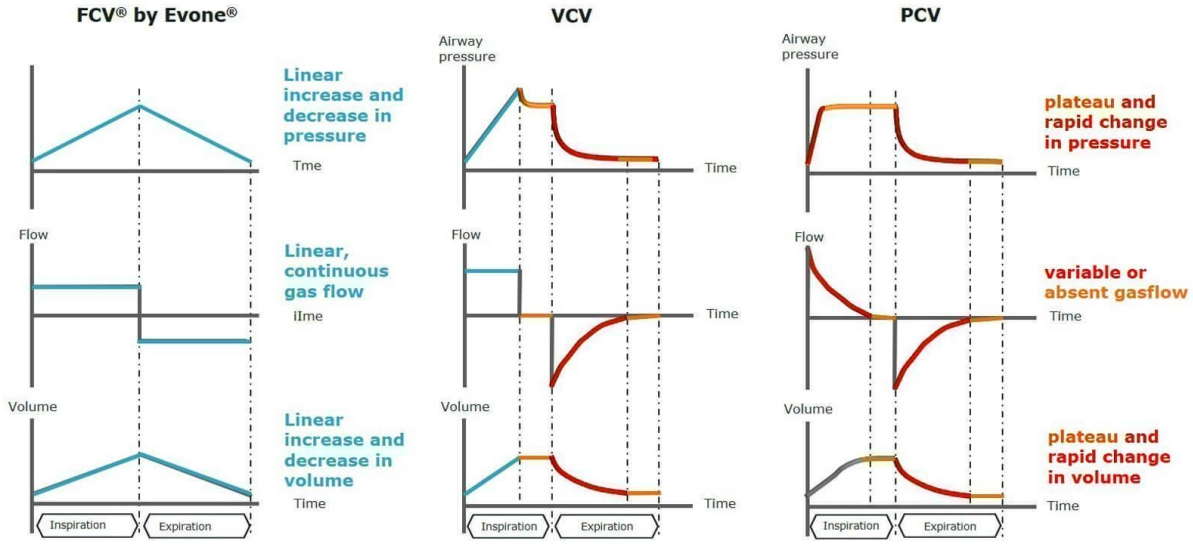


Figure 1. FCV has linear pressure, flow and volume changes in inspiration and expiration. Both VCV and PCV have variable flow and volume changes, periods with no flow and rapid pressure drops especially in exhalation. From Grassetto A, et al. doi: 10.1186/s44158-022-00066-3.

Optimizing intraoperative ventilation is crucial for patients undergoing general anesthesia, where normal physiologic breathing is replaced by non-physiologic mechanical ventilation. This becomes especially challenging in robot-assisted laparoscopic surgeries due to the unique factors involved, such as changes in respiratory system compliance and associated issues with gas exchange.[4] These problems arise largely from the effects of pneumoperitoneum, i.e., the inflation of the abdomen with gas, and the often extreme body positioning required, all to facilitate the surgical intervention but further impairing respiratory mechanics, and increasing the risk and amount of atelectatic lung tissue during intraoperative ventilation. Over the past years, intraoperative lung-protection ventilation strategies have steadily evolved to reduce the risk of atelectasis, in a way to improve postoperative outcomes.[5, 6] Despite these efforts, lung injury, specifically postoperative pulmonary complications (PPCs) remain common.[7, 8] Besides, lung-protection ventilation strategies that use high airway pressures come with important side effects, including hemodynamic instability.[9–11]

Current guidelines for intraoperative ventilation recommend low tidal volume ventilation (6 to 8 ml/kg predicted body weight), even though the superiority of this approach has been questioned recently.[5] While low tidal volume ventilation may help protect the lungs against volutrauma, it may also increase the risk of atelectasis.[12, 13] The driving pressure emerged as an independent predictor of PPCs.[14, 15]

FCV has demonstrated beneficial physiologic effects in animal and small–sized human studies.[1–3, 16–21] In large animal experiments, FCV was shown to enhance lung function, improve lung recruitment,

promote more uniform ventilation, and reduce lung tissue inflammation in an acute respiratory distress syndrome model compared to standard ventilation methods.[3, 21, 22] In cross-over studies involving healthy individuals and obese patients, FCV demonstrated better oxygenation, carbon dioxide removal, and regional ventilation distribution than conventional VCV. [16] Although single-center clinical trials have demonstrated FCV to be safe and feasible, evidence is lacking for its consistent application and clinical benefit across multiple centers, especially for patients undergoing robot-assisted laparoscopic surgery. Without randomized clinical trials, it remains unclear whether FCV is a viable approach for these patients or if respiratory complication rates are comparable to those seen with conventional ventilation methods. Additionally, studies evaluating the safety and feasibility of FCV are needed to inform the design of larger randomized clinical trials.

Therefore, this proposed international multicenter randomized clinical *pilot* trial will evaluate the safety and feasibility of FCV in patients undergoing robot-assisted laparoscopic surgery.

5. STUDY OBJECTIVES

Hypothesis

FCV is a safe and feasible ventilation strategy in patients undergoing robot–assisted laparoscopic surgery.

Overall objective

This *pilot* trial is designed to test the safety (regarding the effects of mechanical ventilation on vital parameters, hemodynamics, and respiratory complications, compared to events/values that are expected during conventional ventilation) and feasibility (regarding the comparability of the application of the ventilation strategy, setting of ventilation parameters, and adherence to the SOPs) of FCV, to test the feasibility of the study protocol and electronic case report form (eCRF), to inform the design of a future randomized clinical trial testing the efficacy of FCV with regard to postoperative outcomes, including postoperative pulmonary complications (PPCs).

Primary objective

The primary objective of this *pilot* trial is to evaluate the *safety* of intraoperative FCV in patients undergoing robot-assisted laparoscopic surgery. Herein we focus on: • gas exchange, including both oxygenation and decarboxylation;

- minute ventilation, during all phases of intraoperative ventilation;
- key ventilator settings and ventilation parameters;
- respiratory complications, including pneumothorax *and*
- hemodynamic complications, including hypotension and arrhythmias.

Secondary objectives

Secondary objectives of this *pilot* trial are to assess the *feasibility* of intraoperative FCV in patients undergoing robot-assisted laparoscopic surgery, the *feasibility* of the study protocol and its eCRF. Herein we focus on:

- the need for rescue ventilation strategies, i.e., whether FCV (as well as PCV) can be used during all phases of intraoperative ventilation; *and*
- compliance with the study protocol, omissions in the eCRF, and the feasibility of follow–up, i.e., how well each PPC can be captured.

Explorative objective

Another secondary objective concerns the primary endpoint of a future randomized clinical trial testing the efficacy of FCV, i.e., its effects on postoperative pulmonary complications. Herein we will focus on: the incidence of PPCs in the FCV group and the PCV group, to inform the sample size calculation of the future trial.

6. STUDY OUTCOMES

Primary outcome

The primary outcome of this *pilot* trial is a set of safety parameters for FCV, including the following:

- 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 PIP, FiO_2, driving pressure and mechanical power of ventilation, and respiratory system compliance and elastance;
- intraoperative respiratory complications;

- (any time point) pneumothorax.
- intraoperative hemodynamic complications:
- (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 anesthesiologic interventions, according to the attending anesthesiologist); *and*
- (hourly) vasopressor support and dose; *and*
- (any time point) occurrence of arrhythmias, and intervention for arrhythmias.

Secondary Outcome

The secondary outcomes focus on evaluating the feasibility of FCV and the study protocol, including the following:

- the need for rescue measures, i.e., whether the ventilation strategy must be stopped or significantly adjusted:
- (in the FCV group) due to device deficiencies (including hardware or software malfunctions requiring replacing the ventilator);
- (in both groups) rescue strategies for predefined events (see chapter 9.);
- rescues for desaturations (i.e., SpO_2 < 92%); *and*
- rescues for insufficient minute ventilation (insufficient decarboxylation, i.e., $etCO_2$ >5.8 kPa).
- feasibility of the study protocol and study procedures:
- compliance with the study protocol, *and*
- feasibility of follow–up (how well each PPC can be captured); *and*
- completeness and omissions in the eCRF.

Explorative secondary outcomes

We will determine the incidence of the PPCs within the first seven postoperative days and compare the incidences between the FCV and the PCV group. PPCs include:

- mild respiratory failure, defined as the occurrence of one or multiple of the following conditions:
- the occurrence of oxygen saturation (SpO_2) < 90% or partial pressure of oxygen in the arterial blood (PaO_2) < 7.9 kPa (or < 50 mm Hg) in room air, but responding to supplemental oxygen;
- a sudden increase in supplemental oxygen requirement to maintain adequate saturation (SpO_2 > 90%) in patients receiving routine postoperative oxygen therapy;
- any level of supplemental oxygen after more than two days postoperatively;
- severe respiratory failure, defined as need for noninvasive or invasive mechanical ventilation, or a PaO_2 < 60 mm Hg (or < 7.9 kPa) or SpO_2 < 90% despite supplemental oxygen in spontaneously breathing patients;
- dyspnea, defined as the patient`s perception of an uncomfortable abnormal awareness of breathing or respiratory limitation (shortness of breath, inability to take a deep breath, or chest tightness);
- productive cough, defined as cough that produces sputum or mucus;
- bronchospasm, defined as newly detected expiratory wheezing treated with bronchodilators;
- suspected pulmonary infection, defined as receiving antibiotics and meeting at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest radiograph when clinically indicated, tympanic temperature > 38.3°C, white blood cell count > 12,000/µL;
- pulmonary infiltrate, defined as any unilateral or bilateral infiltrates on chest radiography;
- aspiration pneumonitis, defined as respiratory failure after the inhalation of regurgitated gastric contents;
- atelectasis, defined as lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non–atelectatic lung on chest radiography;
- ARDS (according to the new global definition of ARDS);[23]

- pleural effusion, defined as blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows on chest radiography;
- pneumothorax, defined as air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiography;
- cardiopulmonary edema, defined as clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest radiograph demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates; *and*
- death in hospital (defined as death from any cause during hospitalization).

7. STUDY DESIGN

Rationale and justification of conducting a pilot trial

Small animal and human studies have demonstrated the promising respiratory benefits of FCV. 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 safety (regarding the effects of mechanical ventilation on vital parameters, hemodynamics, and respiratory complications, compared to events/values that are expected during conventional ventilation) and feasibility (regarding the comparability of the application of the ventilation strategy, setting of ventilation parameters, and adherence to the SOPs) of FCV in patients undergoing robot-assisted laparoscopic surgeries, such as those in the abdominal, urologic, or gynecologic areas. By ensuring its safety and feasibility 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 safety and feasibility of FCV, and its findings will be used to inform the design of a future trial testing the 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, date of birth, height, weight, BMI, date of surgery, indication of surgery, ASA score, ARISCAT 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 PCV during robot-assisted laparoscopic surgery. Patients, randomly assigned to one study group, will be surveyed for the duration of hospitalization (until POD7 or until discharge). Events complying with the respective outcomes and reporting of serious adverse events (SAE) are monitored. The population to be studied in the *pilot* trial will include 70 patients undergoing robot-assisted laparoscopic surgery at the respective participating center.

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.
Attrition Bias: To minimize loss-to-follow-up, evaluation of medical records (information to be obtained include data until end of the study period) will be performed.

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 PCV 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 singleblinded design.

Unblinding Procedures (Code break)

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

8. STUDY POPULATION

Patients scheduled for robot-assisted laparoscopic surgery and at increased risk of developing PPCs will be enrolled. Patients are assessed for the risk of PPCs by using the ARISCAT risk score for PPCs, [24] or a combination of inclusion criteria as recently used in a recent randomized clinical trial of ventilation in patients undergoing major surgery. [25] Patients will be included in selected centers in Switzerland (St. Gallen, Luzerne) .

Eligibility criteria

Inclusion criteria:

- undergoing elective robot-assisted laparoscopic surgery in supine or Trendelenburg position (either abdominal, urologic or gynecologic surgery);
- **AND** increased risk of PPCs according to the ARISCAT risk score (≥ 26 points);
- **OR** the combination of age > 40 years, scheduled surgery lasting > 2 hours and planned to receive an intra-arterial catheter for blood pressure monitoring during the surgery;
- aged ≥ 18 years; 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:

- ideal body weight < 40 kg;
- ASA Physical Status Classification System score IV – VI;
- previous enrolment into the current study;
- being the study investigator, 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 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.

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. 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 regularly takes place, at least 24 hours (but regularly 1-2 weeks) 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 or his designee at the same time point as the participant sign. 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 who are planned to undergo elective robot-assisted laparoscopic surgery (abdominal, urologic, gynecologic surgery) at the participating centers will be informed of the potential for participation in the study during the preoperative anesthesia evaluation or in the course of 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 was 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. Patients denying inclusion to the study will be documented as patients denying inclusion.

Inclusion of vulnerable participants is not intended in this study.

Assignment to study groups
Patients given their informed consent will be randomly assigned 1:1 to either the “FCV” or the “PCV” 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 subjects
The criteria for withdrawal of participants is the request of participants to be withdrawn from the study. 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 Ppeak, 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 PCV with standard PEEP. Detailed information on the two ventilation strategies is provided thereafter.

General anesthesiology procedures
Randomized assignment to the study groups will be conducted after inclusion of the patient. The individual assignment will be known by the attending anesthesiologist to prepare the respective ventilator. After induction of general anesthesia, intubation and ventilation with a conventional tube and ventilator will be maintained until steady state parameters (adequate oxygenation (SpO_2 >92%) have been achieved. Routine general anesthesia is performed according to the specific expertise and routine clinical use of each center. General anesthesia will be inducted and maintained by using total intravenous anesthesia (TIVA) in both groups. TIVA, the standard of care for robot-assisted laparoscopic 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 bundles

The intraoperative ventilation strategies to be studied and the respective settings are summarized in this table.

	FCV	PCV
Ventilator	EVONE	standard operating room ventilator
Mode	flow–controlled	pressure–controlled
V_T	–	7 to 9 ml/kg PBW
RR	–	target $etCO_2$ 4.5 to 5.8 kPa
Flow	target $etCO_2$ 4.5 to 5.8 kPa	–
I:E ratio	1:1	1:1 to 1:2
ΔP	compliance–guided titration	target V_T 7 to 9 ml/kg PBW
PEEP	compliance–guided titration	5 to 10 cmH_2O

Rescue strategies		
Desaturation (SpO_2 < 92%)	1. increase FiO_2 2. increase PEEP	1. increase FiO_2 2. increase PEEP + RM
Further issues	1. according to FCV SOP 2. switch to standard ventilator	1. according to PCV SOP

FiO_2 SpO_2 >=	92%
$etCO_2$ target	$etCO_2$ 4.5 to 5.8 kPa
MAP >=	65mmHg
Anesthesia TIVA	
Neuro Monitoring	BIS
NMT TOF =	0; (extubation TOF > 0.9)
Tube ID male =	8mm; female = 7mm

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 (VT) (i.e. measured VT > expected VT 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%. Rescue to PCV 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: PCV

In the PCV group, intraoperative ventilation will be provided by a standard anesthesia ventilator in use in the respective participating centers. Patients will be ventilated in PCV mode, at the lowest inspired oxygen fraction (FiO_2), 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. Inspiratory to expiratory ratio is set at 1:1 to 1:2, respiratory rate will be adjusted to target normocapnia (target etCO2 4.5 to 5.8 kPa. VT will be set at 7 to 9 ml/kg predicted body weight (PBW). 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 starts with 5 cm H_2O PEEP, and can be increased to 10 cm H_2O PEEP. 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.

Abdominal insufflation

Abdominal insufflation, as part of laparoscopic, robot-assisted surgery, is performed by the attending surgeon or anesthesiologist. The level of applied intra–abdominal 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.

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/):

- 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);
- 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 subjects

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. Non-electronic data will be stored in the study administration office. 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 PCV may be considered. Recruitment maneuvers are possible during PCV, based on the decision of the attending anesthesiologist;
- Impaired elimination of CO_2: if not due to emphysema during abdominal insufflation or airway problems: in the FCV group, flow can be increased stepwise (+1 L/min) to increase minute volume; in the PCV 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 in the PCV group are performed or the fraction of inspired oxygen (FiO_2) is increased, based on the decision of the attending anesthesiologist.

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[26];
- 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 parameters will be documented in the eCRF:

- evaluation of eligibility and inclusion/exclusion criteria during the preoperative anesthesia consultation;
- definition of comparable baseline parameters in regard of risk of PPC with the ARISCAT Assessment Tool and general parameters (including, but not limited to age, gender, weight/height/BMI, type of surgery, pulmonary disease (COPD), smoking status, baseline oxygenation (SpO_2))

Note: Since robot-assisted laparoscopic procedures are always classified as 'peripheral' incisions — assigned '0 points' in the ARISCAT score — this value will not be recorded in the CRF.

Assessment of Primary Outcome

To evaluate the safety of intraoperative FCV, the following parameters will be documented in the eCRF:

- 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 PIP, FiO_2, driving pressure and mechanical power of ventilation, and respiratory system compliance and elastance;
- intraoperative respiratory complications;
- (any time point) pneumothorax.
- intraoperative hemodynamic complications:
- (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 anesthesiologic interventions, according to the attending anesthesiologist); *and*
- (hourly) vasopressor support and dose; *and*
- (any time point) occurrence of arrhythmias, and intervention for arrhythmias.

Assessment of Secondary Outcomes

To test the feasibility of intraoperative FCV and the study protocol, the following parameters will be documented in the eCRF:

- the need for rescue measures, i.e., whether the ventilation strategy must be stopped or significantly adjusted:
- (in the FCV group) due to device deficiencies (including hardware or software malfunctions requiring replacing the ventilator);
- (in both groups) rescue strategies for predefined events (see chapter 9.);
- rescues for desaturations (i.e., SpO_2 < 92%); *and*
- rescues for insufficient minute ventilation (insufficient decarboxylation, i.e., $etCO_2$ >5.8 kPa).
- feasibility of the study protocol and study procedures:
- compliance with the study protocol, *and*
- feasibility of follow–up (how well each PPC can be captured); *and*
- completeness and omissions in the eCRF.

Assessment of explorative secondary outcomes

To determine the incidence of the PPCs within the first seven postoperative days the following parameters will be documented in the eCRF:

- mild respiratory failure, defined as the occurrence of one or multiple of the following conditions:
- the occurrence of oxygen saturation (SpO_2) < 90% or partial pressure of oxygen in the arterial blood (PaO_2) < 7.9 kPa (or < 50 mm Hg) in room air, but responding to supplemental oxygen;
- a sudden increase in supplemental oxygen requirement to maintain adequate saturation (SpO_2 > 90%) in patients receiving routine postoperative oxygen therapy;
- any level of supplemental oxygen after more than two days postoperatively;
- severe respiratory failure, defined as need for noninvasive or invasive mechanical ventilation, or a PaO_2 < 60 mm Hg (or < 7.9 kPa) or SpO_2 < 90% despite supplemental oxygen in spontaneously breathing patients;

- dyspnea, defined as the patient`s perception of an uncomfortable abnormal awareness of breathing or respiratory limitation (shortness of breath, inability to take a deep breath, or chest tightness);
- productive cough, defined as cough that produces sputum or mucus;
- bronchospasm, defined as newly detected expiratory wheezing treated with bronchodilators;
- suspected pulmonary infection, defined as receiving antibiotics and meeting at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest radiograph when clinically indicated, tympanic temperature > 38.3°C, white blood cell count > 12,000/µL;
- pulmonary infiltrate, defined as any unilateral or bilateral infiltrates on chest radiography;
- aspiration pneumonitis, defined as respiratory failure after the inhalation of regurgitated gastric contents;
- atelectasis, defined as lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non–atelectatic lung on chest radiography;
- ARDS (according to the new global definition of ARDS);[23]
- pleural effusion, defined as blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows on chest radiography;
- pneumothorax, defined as air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiography;
- cardiopulmonary edema, defined as clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest radiograph demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates; *and*
- death in hospital (defined as death from any cause during hospitalization).

Assessments in subjects 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 subjects after the regular termination of the study
The follow-up of the study will be until POD7 or until the patient leaves the hospital. 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	
POD	Preoperative		POD0							POD 1-7	discharge
Time			T-1	T0	T+1	T+2	T+X (each hour until end of surgery)	T+Y extubation	T postop		
Enrolment											

Eligibility	+										
IC	+										
Randomization		+									
Baseline & Scores											
Sex, Age, height, weight, BMI, Smoker	+										
ASA Score	+										
ARISCAT Score	+										
Intervention											
FCV				+	+	+	+				
PCV				+	+	+	+				
Primary Outcome											
Safety			+	+	+	+	+				
Secondary & Explorative Secondary Outcomes											
Feasibility				+	+	+	+	+	+	+	
PPCs								+	+	+	+
Safety											
AE/SAE			+	+	+	+	+	+	+	+	+

11. STATISTICS AND METHODOLOGY

Hypothesis

FCV is a safe and feasible ventilation strategy in patients undergoing robot–assisted laparoscopic surgery.

Determination of Sample Size

To estimate the appropriate sample size for this *pilot* trial, we considered both safety and feasibility across multiple centers. Assuming a target of 10 to 15 participants per randomization group in each of the four centers, the total sample size would range from 80 to 120 participants (4 centers × 10–15 participants × 2 randomization groups). For practical purposes and to ensure a robust assessment of the trial's objectives, we have selected a total sample size of 70 participants in Switzerland (with 30-60 patients being investigated in additional European centers in a separate, but identical study (due to regulatory aspects of the participating countries)). This number balances logistical feasibility with the need for adequate data to assess safety outcomes.

This *pilot* trial primarily aims to assess the safety of the FCV strategy in patients scheduled for robot–assisted laparoscopic abdominal, urologic, or gynecologic surgery, and evaluate its feasibility. Additionally, the incidence of postoperative pulmonary complications in this *pilot* trial 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 detected any impact of clinical outcomes.

Statistical criteria of termination of the study

Not applicable.

Planned Analyses

Balance between study groups will be ensured by randomization and an appropriate sample size.

Baseline characteristics will be assessed by appropriate tests to demonstrate balance between groups. We will primarily perform an intention to treat analysis, and will add a per protocol analysis as sensitivity analysis. Tests for normal distribution of the data will include QQ-plot assessments. Potential differences between the two groups in the distribution of dichotomous data are analyzed by chi2 statistics. Continuous data are analyzed by parametric (t-test, ANOVA) or non-parametric (Mann-Whitney U) test for unpaired comparison as appropriate. A sub-analysis related to sex, age, type of surgery will be performed for all study endpoints.

Datasets to be analyzed, analysis populations

All participants will be analyzed in terms of the respective endpoint parameters. The data of patients who leave the study prematurely are analyzed independently of the completion of the study (intention to treat). A subgroup analysis with respect to sex, age, type of surgery will be performed for all study endpoints.

Primary Analysis

The data analysis of the primary endpoint will be evaluated using chi^2 statistics. The data analysis will be performed after completion of the study period, i.e. after the 7^{th} postoperative day or discharge, whatever comes first.

Secondary and Exploratory Analyses

The data analysis of the secondary endpoints will be evaluated using chi^2 statistics and parametric (ttest, ANOVA) or non-parametric (Mann-Whitney U) test for unpaired comparison as appropriate. The data analysis will be performed after completion of the study period, i.e. after the 7^{th} postoperative day or discharge, whatever comes first.

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.

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 subject administered a study intervention which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable 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 and the Investigatorof 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 subject, does not influence treatment, usually does not require intervention
Moderate	Event may cause discomfort that interferes with usual activities or be dangerous for the subject; intervention may be needed.
Severe	Event may cause noticeable disability; subject 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, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Both ventilation strategies (FCV & PCV) 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 Serious Adverse Events (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 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 subjects 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 study leader 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 ASR.

Notification and reporting upon completion, discontinuation or interruption
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.
- 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, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

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.

13. FURTHER ASPECTS

Overall ethical considerations

The aim of this *pilot* trial is to investigate the safety and feasibility of FVC in patients undergoing robotassisted laparoscopic abdominal, urologic and gynecologic 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. Therefore, we find it appropriate to compare FCV with existing strategies such as PCV, as we anticipate meaningful improvements in patient outcomes with minimal additional risk.

14. QUALITY CONTROL AND DATA PROTECTION

Data handling and record keeping / archiving

Data collected will be documented and stored in an electronic data system (electronic case report form (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, and ARISCAT score
- primary outcome parameters (safety)
- secondary outcome parameters (feasibility)
- other secondary outcome parameters (PPCs)
- serious adverse events (defined in section 10)
- additional comments

Perioperative vital parameters (continuous parameters, i.e.: blood pressure, heart rate, oxygen saturation, etc.) will be documented in the (electronic) anesthesia protocol.

Note: Since robot-assisted laparoscopic procedures are always classified as 'peripheral' incisions — assigned '0 points' in the ARISCAT score — this value will not be recorded in the CRF.

Specification of source data and source documents

Electronic sources of data include the electronic medical documentation systems (compliant to GCP).

Archiving of essential study documents

All the documents of the study must be archived for a minimum of 20 years after regular or premature termination of the study.

Data management

All data collected will be stored in the eCRF on a password protected server (Castor EDC (Electronic Data Capture), provided by Castor) (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 and Lucerne will be performed by the CTU St. Gallen according to a Monitoring Plan provided by the Clinical Trials Unit. 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 subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality shall be protected by assigning each participant a unique numerical identifier to be used in lieu of their name in the study database. 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. If sex and gender effects are observed, they will be published in the final study report. A summary of the results for the general public will be uploaded to BASEC within one year of the study's completion. 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). This study protocol and the pseudonymized raw dataset will be published as well. The publication process shall be under the direction of the sponsor.

16. REFERENCES

- Declaration of Helsinki https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medicalresearch-involving-human-subjects/
- Federal Act on Data Protection (FADP) https://www.admin.ch/opc/en/classified-compilation/19920153/index.html
- Human Research Act (HRA) https://www.admin.ch/opc/de/classified-compilation/20061313/index.html
- International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
- Ordinance on Clinical Trials in Human Research (ClinO) https://www.admin.ch/opc/de/classified-compilation/20121176/index.html

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18. APPENDICES

Guidelines used in the trial and referenced aboved

o ERAS (Gynecology 2019 update; Abdominal 2018; Urologic 2013 - http://erassociety.org/guidelines/list-of-guidelines/)

o Safe Surgery Checklist from the World Health Organization (Safe surgery [www.who.int], revised Version 1, 2009) o Advanced Cardiac Vascular Life Support Guidelines from 2015 [26] o The new global definition of ARDS from 2024 [23] o ARISCAT risk score from 2010 [24]