Statistical Analysis Plan

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

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Study Investigators: The PROFLOW–ROBOTic Investigators

Correspondence
Timur Yurttas, MD
Department of Anesthesiology, Rescue– and Pain Medicine
Cantonal Hospital of St. Gallen, HOCH Health Ostschweiz
St. Gallen
Switzerland
Email: timur.yurttas@h-och.ch

Introduction

The 'PROtective ventilation with FLOW–controlled ventilation to improve postoperative pulmonary outcome after ROBOT–assisted laparoscopic surgery *pilot*' (PROFLOW–ROBOTic *pilot*) trial was designed to evaluate the safety and feasibility of a ventilation bundle incorporating flow–controlled ventilation (FCV) with compliance–guided titration of positive end–expiratory pressure (PEEP) and driving pressure (ΔP) in patients planned for robot–assisted laparoscopic surgery.[1] This *pilot* study further determined the feasibility of the study protocol, and explored the incidence of postoperative pulmonary complications (PPCs) during the first seven postoperative days, to inform the design of a future larger randomized clinical trial. This statistical analysis plan (SAP) describes the predefined analyses for the 'PROFLOW–ROBOTic *pilot*' trial prior to database lock and commencement of analyses.

Methods

Design

'PROFLOW–ROBOTic *pilot*' is an international multicenter randomized clinical pilot trial comparing intraoperative FCV with conventional PCV in patients undergoing robot–assisted laparoscopic surgery. The study was conducted in three hospitals in three Switzerland, Germany and Austria, and was completed after enrolling a total of 100 patients. Ethical approval was obtained from Ethics Committee Eastern Switzerland, St. Gallen, Switzerland (EKOS 24/197), and thereafter in the two additional hospitals. All patients had to provide signed informed consent before start of any study–related measure.

Patients

'PROFLOW–ROBOTic *pilot*' included adult patients (≥18 years), planned for elective robot–assisted laparoscopic abdominal, urological, or gynecological surgery in supine or Trendelenburg position. Eligible patients had to have an increased risk for PPCs, defined as an 'Assess Respiratory Risk in Surgical Patients in Catalonia' (ARISCAT) score ≥ 26, or fulfilment of all of the following criteria: age >40 years, expected surgery duration >2 hours, and planned intra–arterial blood pressure monitoring.

Patients were excluded if body weight was < 40 kg, American Society of Anesthesiologists (ASA) score was > III, pregnancy or lactation was present, no written informed consent was obtained, being the investigator/family

member/employee/dependent person, if the enrolment in another interventional study was present, or if they had previously participated in the study.

Randomization and blinding

Patients were randomly assigned in a 1:1 ratio to receive either FCV or PCV using a centralized electronic randomization module. Randomization was stratified by participating center using permuted blocks of varying size. Patients remained blinded to treatment allocation. Due to the nature of the intervention, healthcare professionals responsible for intraoperative management could not be blinded.

Collected data

Baseline variables collected prior to surgery included age, sex, height, weight, body mass index (BMI), ASA score, ARISCAT score, smoking status, pulmonary comorbidities, baseline oxygenation, and type of surgery.

During anesthesia, ventilatory and physiological variables were recorded after induction, after completion of pneumoperitoneum and surgical positioning, and hourly thereafter until the end of surgery. Collected variables included tidal volume (V_T), respiratory rate, minute ventilation, peak inspiratory pressure, PEEP, ΔP, inspiratory–to–expiratory ratio, FiO_2, oxygen saturation, end–tidal carbon dioxide concentration, arterial blood gas values when available, C_{RS}, and hemodynamic variables.

Postoperatively, patients were followed daily for up to seven days or until hospital discharge, whichever occurred first, to assess PPCs and other study outcomes.

Study interventions

Patients in both groups received general anesthesia using total intravenous anesthesia according to local clinical practice.

In the FCV group, ventilation was performed using the EVONE® ventilator (IES Ventinova Medical, Derio, Spain). PEEP and inspiratory pressure were titrated according to dynamic compliance to determine the PEEP and ΔP associated with the highest compliance and tidal volume. The inspiratory–to–expiratory ratio was fixed at 1:1. Flow was adjusted to maintain normocapnia and FiO_2 adjusted to maintain adequate oxygenation.

In the PCV group, patients received conventional lung–protective pressure–controlled ventilation using the standard anesthesia ventilator available at the participating center. V_T was targeted at 7–9 ml/kg predicted body weight, PEEP was

maintained between 5 and 10 cm H_2O, respiratory rate was adjusted to maintain normocapnia, and FiO_2 adjusted to maintain adequate oxygenation.

Rescue conversion was permitted when considered necessary for patient safety. In the FCV group, rescue conversion to conventional ventilation was allowed. In the PCV group, rescue to FCV was not allowed, while rescue to another conventional ventilation mode was permitted.

Primary and secondary outcomes

The primary endpoint of this pilot trial is the safety of the respective ventilation bundle. This safety endpoint includes various factors:

- hourly gas exchange parameters:
  - PaO_2;
  - $PaCO_2$;
  - SpO_2; *and*
  - end–tidal CO_2.
- hourly ventilation variables:
  - minute ventilation;
  - V_T;
  - respiratory rate;
  - PEEP;
  - peak inspiratory pressure;
  - ΔP;
  - mechanical power; and
  - C_{RS}.
- respiratory complications, at any time, and including but not limited to:
  - pneumothorax.
- hemodynamic complications:
  - hypotension at any timepoint;
  - vasopressor support and dose hourly; *and*
  - arrhythmias and interventions at any timepoint.

Secondary outcomes

Secondary endpoints evaluate the feasibility of the ventilation protocol, and compliance with the study protocol.

Ventilation protocol endpoints include:

- major deviations from the ventilation protocol;

    - changes made to the ventilation strategy (i.e., deviations from the settings (i.e., V_T ranges, PEEP levels) defined in the respective ventilation protocol for FCV and PCV, or non–adherence to the compliance–guided titration strategy in FCV) for any other reason than pre–approved protocol deviations;
    - any deviation from the allocated ventilation mode (i.e., start with PCV, or a switch from FCV to PCV in the FCV group, or start with FCV, or a switch from PCV to FCV in the PCV group) for any other reason than pre–approved protocol deviations;
- requirement for rescue interventions; *and*
- minor deviations from the ventilation protocol
    - any pre–approved protocol deviations.

Study protocol endpoints include:

- any deviation from the study protocol;
- completeness of intraoperative data collection;
- completeness of eCRF data; *and*
- completeness of postoperative PPC follow–up.

Exploratory outcomes

Exploratory outcomes concerned PPCs occurring during the first seven postoperative days or until hospital discharge, whichever occurs first. PPCs will be evaluated using the composite PPC (European Perioperative Clinical Outcome (EPCO) definition) occurrence.

Sample size

The sample size of this analysis is the number of patients included in 'PROFLOW–ROBOTic *pilot*'.

Statistical analysis plan

As this pilot trial was designed to assess primarily the safety and feasibility, rather than efficacy of FCV, analyses of PPC outcomes are exploratory and hypothesis–generating. All analyses will be performed according to the intention–to–treat (ITT) principle. In addition, if at least 2% of patients received the incorrect allocated intervention or had major protocol deviations, a supportive per–protocol analysis, including only patients who received the allocated intervention and had no major protocol deviations, will be performed.

Continuous variables will be reported as mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Categorical variables will be reported as counts and percentages. For comparisons between groups continuous variables will be analyzed using Student's t–test or Mann–Whitney U test, as appropriate. Categorical variables will be analyzed using the Chi–square test or Fisher's exact test. Effect estimates will be reported according to outcome type. Continuous outcomes will be summarized using mean or median differences with 95% confidence intervals, as appropriate. Binary outcomes will be summarized using risk differences with 95% confidence intervals. Ordinal outcomes, including PPC severity according to the 'PrECiSIOn' framework, will be summarized using common odds ratios with 95% confidence intervals from proportional–odds ordinal logistic regression, where appropriate. Feasibility traffic–light criteria will be reported descriptively only. Effect estimates will be presented in the corresponding outcome tables, together with their 95% confidence intervals.

Baseline characteristics will be summarized by randomization group. Variables included are presented in a Table (dummy **Table 1**). No statistical comparisons between groups will be performed.

Safety endpoints (the primary outcome) will be summarized descriptively at each study timepoint and, where appropriate, across the entire intraoperative period in Tables and Figures (dummy **Table 2** and dummy **Figures 1–2**)

Feasibility of the ventilation protocol endpoints (a secondary outcome) will be summarized descriptively as counts and percentages in a Table (dummy **Table 3**) and visualized (dummy **Figure 3**). Ventilation protocol adherence will additionally be evaluated according to the predefined traffic–light criteria:

- Green: ≥80% adherence;
- Amber: 40–79% adherence;
- Red: <40% adherence.

Feasibility of the study protocol (a secondary outcome) will be summarized descriptively as counts and percentages in a Table (dummy **Table 3**) and visualized (dummy **Figure 3**). Study protocol adherence will also be evaluated according to the predefined traffic–light criteria:

- Green: ≥80% adherence;
- Amber: 40–79% adherence;
- Red: <40% adherence.

The incidence of PPCs (an exploratory endpoint) will be assessed during the first seven postoperative days or until hospital discharge, whichever occurs first. PPCs are defined according to EPCO definitions.[2] PPCs will be reported as (1) a composite outcome, (2) individual PPC components, and (3) severity categories according to the 'PrECiSIOn' framework definition.[3] Results will be summarized in (dummy **Table 4** and **Figure 5–6**). Binary outcomes will be presented as counts and percentages with corresponding risk differences and 95% confidence intervals. PPC severity categories according to the 'PrECiSIOn' framework will additionally be summarized using common odds ratios with 95% confidence intervals.

No imputation of missing data will be performed. Available data will be used for all analyses. The amount of missing data will be reported for each outcome whenever applicable. Reasons for missing data, protocol deviations, and losses to follow–up will be summarized descriptively. All analyses will be conducted using R version 4.5.3. Statistical significance is set at $p < 0.05$.

References

1. PROFLOW-ROBOTic Investigators. PROtective ventilation with FLOW–controlled ventilation in ROBOT–assisted laparoscopic surgery (PROFLOW–ROBOTic pilot) — study protocol for an international multicenter pilot randomized clinical trial. *Rev Esp Anestesiol Reanim* 2026; **in press**

2. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions. *European Journal of Anaesthesiology* 2015; **32**: 88–105

3. Nasa P, Yurttas T, Battaglini D, et al. Consensus on the definition, components, timeframe and grading of composite outcome of postoperative pulmonary complication-protocol for an international mixed-method consensus study (PrECiSIOn). *BMJ Open* 2025; **15**: e103888

Tables

Characteristic	FCV (n=)	PCV (n=)
Age, years		
Female sex, n (%)		
Height, cm		
Weight, kg		
Body mass index, kg/m^2		
Predicted body weight, kg		
ASA score, n (%)		
I		
II		
III		
ARISCAT score		
Smoking status, n (%)		
Never		
Former		
Current		
Pack years		
COPD, n (%)		
Baseline SpO_2, %		
Type of surgery, n (%)		
Abdominal		
Urological		
Gynecological		
Duration of ventilation, min		

Table 1: Baseline Characteristics; Data are mean ± standard deviation (SD), median [IQR], or n (%), as appropriate.

Outcome	FCV	PCV	Effect estimate (95% CI)
Gas exchange			
PaO_2			
$PaCO_2$			
SpO2			
End-tidal CO2			
Ventilation variables			
Minute ventilation			
Tidal volume			
Respiratory rate			
PEEP			
Peak inspiratory pressure			
Driving pressure			

Outcome	FCV	PCV	Effect estimate (95% CI)
Mechanical power			
Respiratory system compliance			
Respiratory complications			
Pneumothorax			
Hemodynamic complications			
Hypotension			
Vasopressor use			
Total norepinephrine dose			
Arrhythmia			
Intervention for arrhythmia			

Table 2: Primary (Safety) Outcome (Continuous variables are summarized as mean ± SD or median [IQR] and compared using mean or median differences with 95% confidence intervals. Binary outcomes are summarized as n (%) and compared using risk differences with 95% confidence intervals.)

Outcome	FCV (n =)	PCV (n =)	Total (n =)	Effect estimate (95% CI)
Ventilation protocol feasibility				
Successful completion of allocated ventilation strategy				
Rescue intervention required				
Ventilator replacement required				
Major protocol deviation				
Minor protocol deviation				
Study protocol feasibility				
Study protocol deviation				
Complete intraoperative dataset				
Complete eCRF				
Complete PPC follow-up				
Traffic-light assessment				
Ventilation protocol adherence	Green / Amber / Red	Green / Amber / Red		—
Study protocol adherence	Green / Amber / Red	Green / Amber / Red		—
eCRF completeness	Green / Amber / Red	Green / Amber / Red		—

Table 3: Secondary (Feasibility) Outcomes (Binary outcomes are summarized as n (%) and compared using risk differences with 95% confidence intervals. Traffic-light classifications are descriptive only.)

Outcome	FCV (n =)	PCV (n =)	Effect estimate (95% CI)
EPCO outcomes			
Composite PPC			
Dyspnoea			
Bronchospasm			
Productive cough			
Suspected pulmonary infection			
Pulmonary infiltrate			
Aspiration pneumonitis			
Atelectasis			
Pleural effusion			
Cardiopulmonary oedema			
Pneumothorax			
Mild respiratory failure			
Severe respiratory failure			
Acute respiratory distress syndrome			
In-hospital death			
PrECiSIOn outcomes			
Composite PPC			
Dyspnoea			
Bronchospasm			
Upper airway obstruction			
Tracheobronchitis (requiring medical treatment)			
Atelectasis (requiring intervention)			
Pleural effusion (requiring intervention)			
Pulmonary congestion (requiring intervention)			
Suspected respiratory infection			
Pneumonia			
Aspiration pneumonitis (requiring intervention)			
Mild respiratory failure			
Moderate respiratory failure			
Severe respiratory failure			
Hypercapnic respiratory failure			
Acute respiratory distress syndrome (ARDS)			
Empyema			
Haemothorax (requiring intervention)			
Pneumothorax (requiring intervention)			

Outcome	FCV (n =)	PCV (n =)	Effect estimate (95% CI)
Pulmonary embolism			
Bronchopleural fistula			
Unplanned mechanical ventilation			
Reintubation			
Bronchoscopy			
Surgical re-intervention			
Prolonged hospital stay			
Hospital readmission			
Unplanned ICU (re-)admission			
Death			
PrECiSIOn severity			
No PPC			
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Grade 5			
Grade 6			

Table 4: Exploratory Outcome PPC (Binary outcomes are summarized as n (%) and compared using risk differences with 95% confidence intervals. Ordinal PPC severity categories are summarized as n (%) and compared using the common odds ratio with 95% confidence intervals from a proportional-odds model.)

Figures

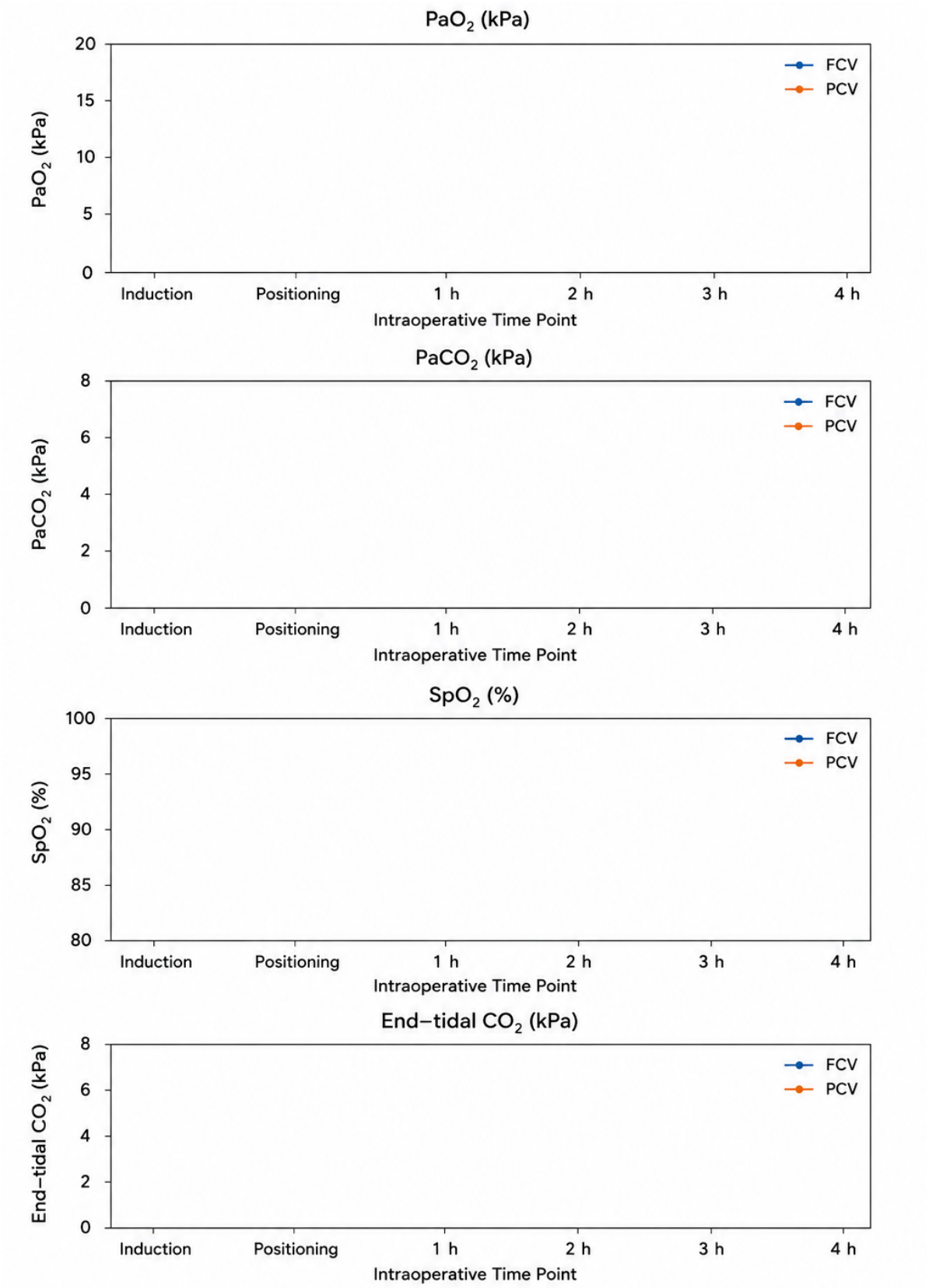


Figure 1: Primary (Safety) Outcome, Gas Exchange

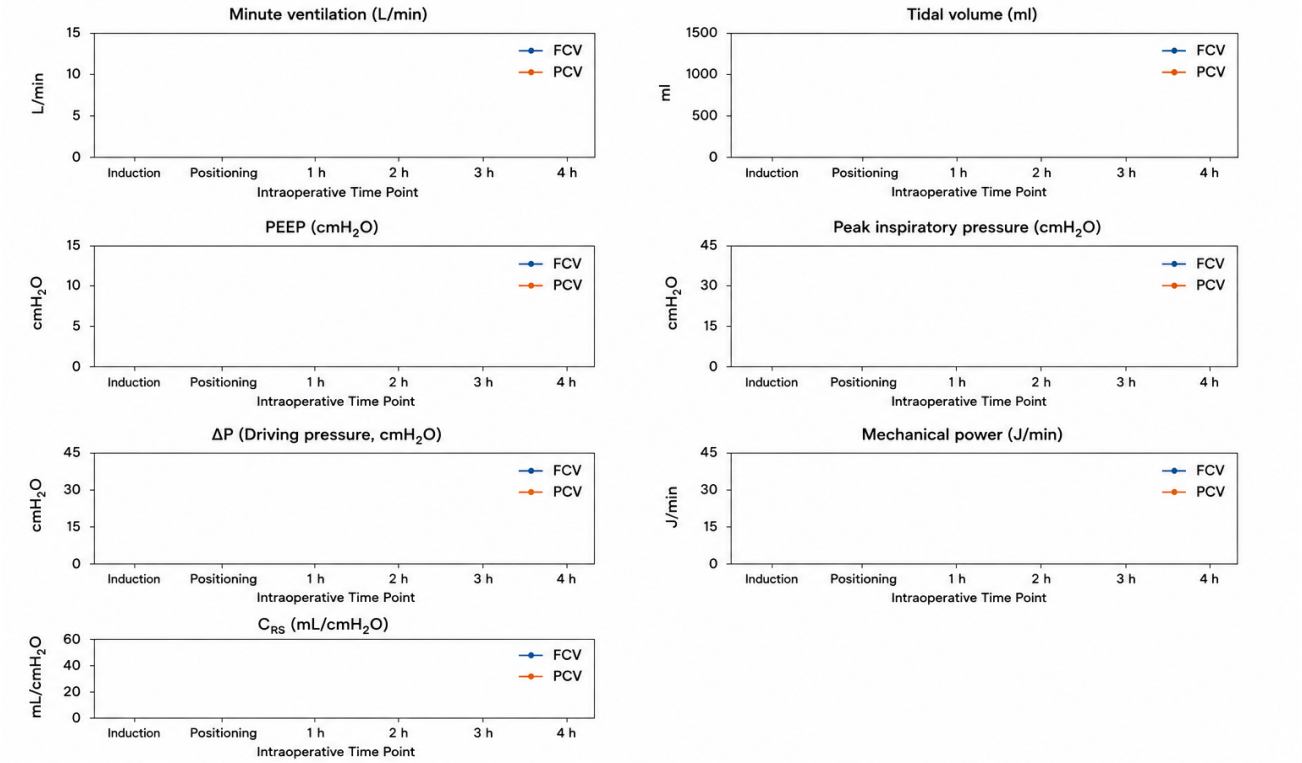


Figure 2: Primary (Safety) Outcome, Respiratory Parameters

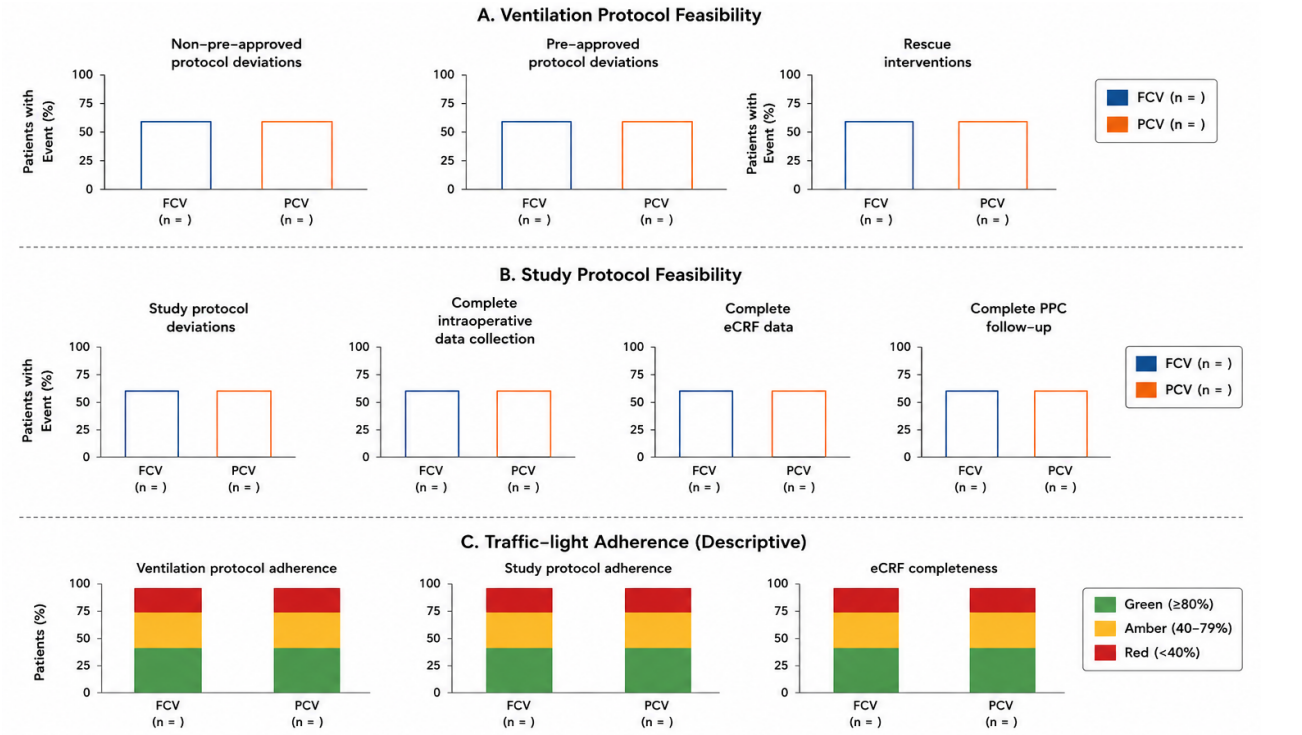


Figure 3: Secondary (Feasibility) Outcomes

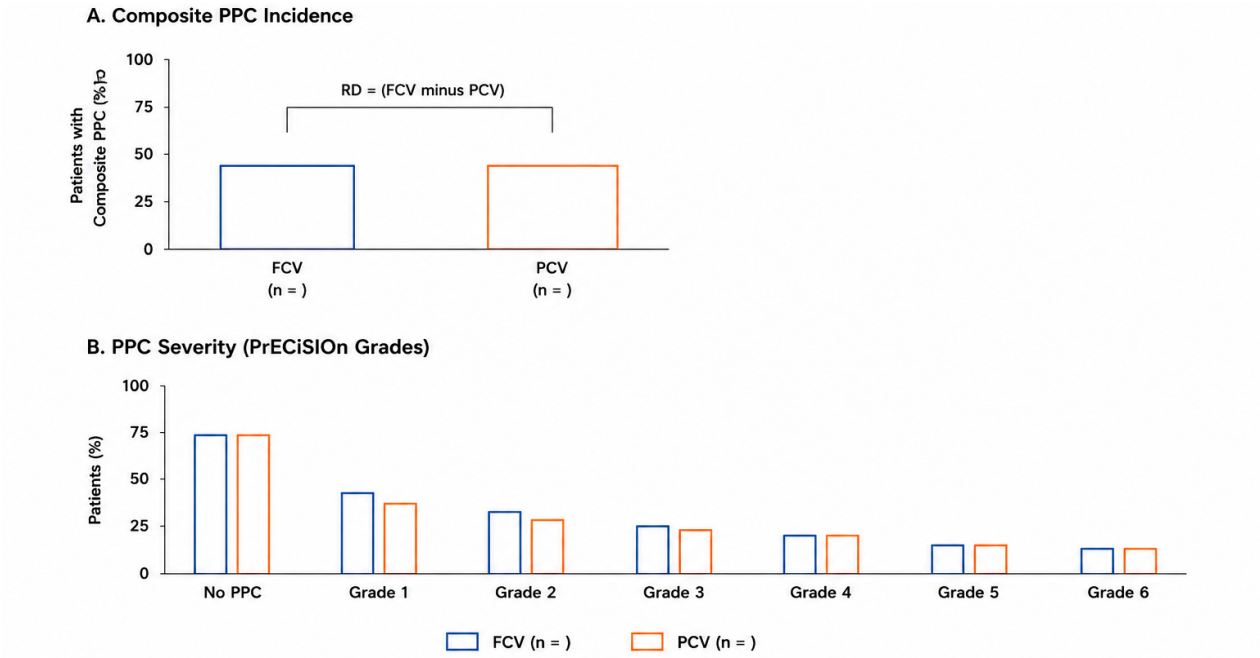


Figure 4: Exploratory Outcome PPC Incidence and Severity Grading