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Rationale and study design for an individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) and its effects on surgical site infection: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Surgical site infection (SSI) is a serious postoperative complication that increases morbidity and healthcare costs. SSIs tend to increase as the partial pressure of tissue oxygen decreases: previous trials have focused on trying to reduce them by comparing high versus conventional inspiratory oxygen fractions (FIO_2) in the perioperative period but did not use a protocolised ventilatory strategy. The open-lung ventilatory approach restores functional lung volume and improves gas exchange, and therefore it may increase the partial pressure of tissue oxygen for a given FIO_2. The trial presented here aims to compare the efficacy of high versus conventional FIO_2 in reducing the overall incidence of SSIs in patients by implementing a protocolised and individualised global approach to perioperative open-lung ventilation.

Methods and analysis This is a comparative, prospective, multicentre, randomised and controlled two-arm trial that will include 756 patients scheduled for abdominal surgery. The patients will be randomised into two groups: (1) a high FIO_2 group (80% oxygen; FIO_2 of 0.80) and (2) a conventional FIO_2 group (30% oxygen; FIO_2 of 0.30). Each group will be assessed intra- and postoperatively. The primary outcome is the appearance of postoperative SSI complications. Secondary outcomes are the appearance of systemic and pulmonary complications.

Ethics and dissemination The iPROVE-O2 trial has been approved by the Ethics Review Board at the reference centre (the Hospital Clínico Universitario in Valencia). Informed consent will be obtained from all patients before their participation. If the approach using high FIO_2 during individualised open-lung ventilation decreases SSIs, use of this method will become standard practice for patients scheduled for future abdominal surgery. Publication of the results is anticipated in early 2019.

Trial registration number NCT02776046; Pre-results.

Strengths and limitations of this study

- To the best of our knowledge, this is the first trial evaluating the efficacy of high FIO_2 versus low FIO_2 percentages to decrease surgical site infections (SSIs) in patients treated by implementing a protocolised and individualised global approach to perioperative open-lung ventilation.
- This trial will also evaluate, for first time, whether the intervention group treated with a high FIO_2 worses postoperative pulmonary function after treatment with this open-lung approach.
- Although the partial pressure of tissue oxygen will not be measured, arterial oxygen pressure will be measured in all patients during the perioperative period.
- The inclusion of surgeries with a very low risk of developing SSIs may jeopardise the results by underestimating the potential benefits of high FIO_2 in a more specific population with a higher risk of developing SSIs.

INTRODUCTION

An estimated 234 million major surgical procedures are performed each year worldwide.[1] Of these, surgical abdominal procedures are associated with high postoperative morbidity and therefore with a negative impact on clinical outcomes and healthcare costs.[2–4] One of the most serious complications in this population is surgical site infection (SSI), with a reported incidence in abdominal surgery of between 10% and 30%.[2 3] In addition, SSIs can also promote other complications such as anastomotic dehiscence, sepsis or septic shock, the need for surgical re-intervention, and death.[5]

Recent trials have focused on perioperative strategies to decrease the incidence of SSIs.[6–10] The primary innate defence against surgical pathogens is mediated by neutrophils which kill the pathogens by oxidative burst: this occurs as a function of the partial pressure of tissue oxygen, which is directly dependent on the partial pressure of arterial oxygen (PaO_2).[11 12] Indeed, several clinical studies have shown that SSIs are related to the perioperative PaO_2.[13–15] Therefore, strategies that enhance the partial pressure of tissue oxygen have shown a decrease of SSIs and improvements in cardiac output, supplemental fluid requirements, and achieving normothermia, pain control and epidural anaesthesia.[6–10]

Supplemental oxygen increases the oxygen saturation of wound tissue by ensuring adequate tissue oxygen perfusion.[16] Hence, several randomised controlled trials have compared high versus conventional FIO_2 with the aim of comparing the effects of different oxygen partial pressures on SSIs.[16–25] However, these randomised controlled trials have so far reported inconsistent results in association with high FIO_2 that show varying benefits,[16–20] no differences[21 22] or even an increased risk of SSIs.[23] A Cochrane review recently concluded that the evidence is insufficient to support a recommendation for the routine use of high FiO_2 in abdominal surgery,[24] although, another meta-analysis showed contradictory results.[26 27] In addition, the WHO recently included the use of 80% perioperative oxygen (an FIO_2 of 0.8) for the prevention of SSIs in its updated guidelines.[28]

The relationship between PaO_2 and FIO_2 in the population of patients with healthy lungs who undergo surgical interventions is mainly affected by pulmonary shunt induced by lung collapse, which causes hypoxaemia and can occur in nearly 90% of patients receiving mechanical ventilation under anaesthesia.[29] Many factors influence the appearance and the magnitude of lung collapse, but an important element is the chosen ventilatory strategy.[30] Robust evidence in the literature has shown that an open-lung strategy, that is, the combination of an alveolar recruitment manoeuvre (ARM) and maintenance of positive end-expiratory pressure (PEEP), reverses and prevents lung collapse.[31–34]

Hypothesis

Based on the above, we hypothesised that compared with a conventional FIO_2, a high FIO_2 would increase the tissue partial pressure of oxygen and thus decrease the incidence of SSIs in patients treated by implementing a protocolised individualised global approach to perioperative open-lung ventilation.

Aim

Therefore, the individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) trial aims to compare the efficacy of high versus conventional FIO_2 in reducing the overall incidence of postoperative SSIs when applied during an individualised perioperative open-lung ventilatory strategy.

Primary outcome

The primary outcome of the iPROVE-O2 trial is the appearance of SSIs in study subjects within the first 7 postoperative days.

METHODS

Study design

The iPROVE-O2 trial is a comparative, prospective, multicentre, randomised and controlled two-arm trial that will include 756 patients (figure 1).

Study population

Inclusion criteria

The study population inclusion criteria are: male or female patients aged ≥18 years with a body mass index (BMI) of <35 kg/m^2, who are scheduled for major abdominal (laparotomy or laparoscopic) surgery with an expected operating time of more than 2 hours.

Exclusion criteria

The exclusion criteria are: age <18 years, pregnancy or breast-feeding status, emergency or acute surgery, moderate or severe acute respiratory distress syndrome (ARDS; PaO_2/FIO_2 <200 mmHg), diagnosis of heart failure (defined as a cardiac index <2.5 mL/min/m^2 or >2.5 when ≥5 µg/kg/min dobutamine is required) or suspected heart failure according to clinical signs (hypotension, oliguria and pulmonary oedema) together with N-terminal pro b-type natriuretic peptide (NT-proBNP) >13 pg/mL, suspected intracranial hypertension (>15 mmHg), presence of pneumothorax or giant bullae on a chest radiograph or CT image, and participation in another interventional study.

Randomisation and bias minimisation method

Informed consent will be obtained from each participant by the principal investigator or a sub-investigator before patient enrolment in the study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be consecutively included and randomised into one of the two study arms by the principal investigator at each study site (figure 1).

The patients will be randomised online via the study's website http://iprove.incliva.es using the Mersenne Twister algorithm with an allocation rate of 1:1. Randomisation will be stratified according to the details set out on

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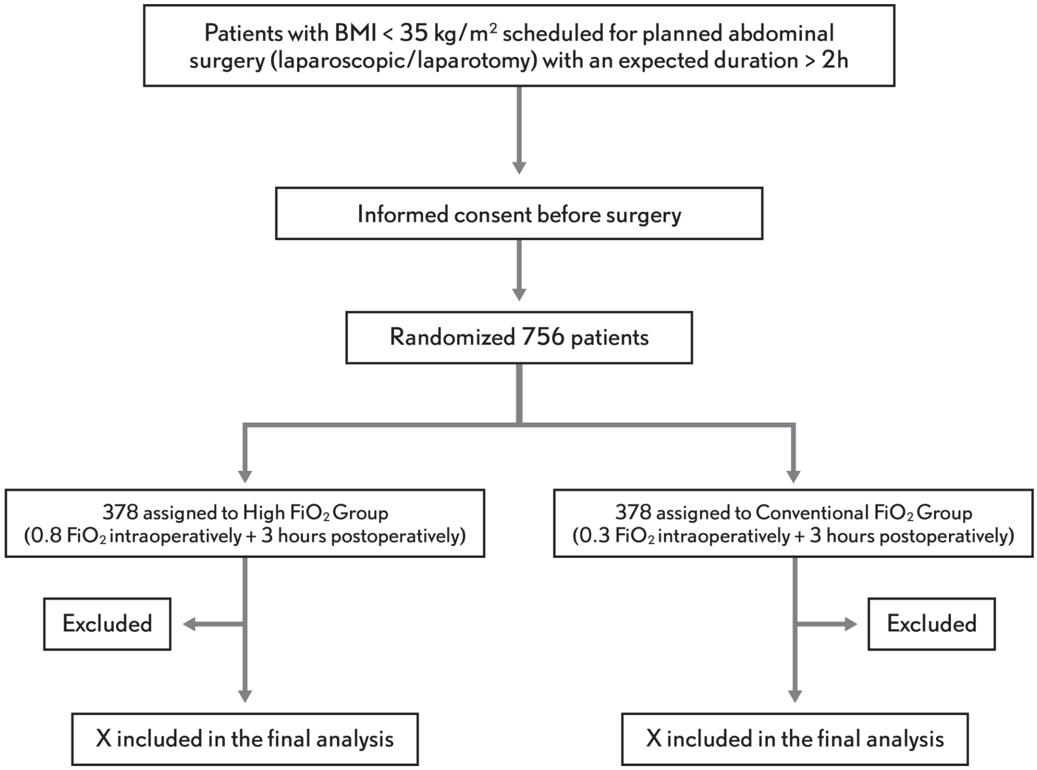

Figure 1 CONSORT flow diagram of iPROVE-O2.

this website. Patients will be allocated to (i) a high FIO_2 group (an FIO_2 of 0.80) or (ii) a conventional FIO_2 group (an FIO_2 of 0.30).

Blinding

Because the study characteristics do not allow blinding of the first investigator in the operating and postoperative room, at least two investigators are required in each participating centre. After 24 hours, all acquired data will be sent to the second investigator who will be blinded to the patient's randomisation arm, and who will have no access to the patient's records from the first 24 hours. In addition, the surgical wound will be evaluated at each participating centre by independent surgeons, also blinded to the randomisation arm. We assume that, because different masks will be used for oxygen administration in each of the study groups in the postoperative period, patient unblinding may occur. However, we anticipate that only a few patients will be able to discern their randomisation arm. Nevertheless, we will register and analyse the number of patients who become aware of their randomisation arm. The blinding of all general procedures and ventilatory management unrelated to FIO_2 have been previously described as part of the individualised perioperative group in the iPROVE study protocol.[35]

General procedures

All participating patients, regardless of the study arm into which they are randomised, will be monitored and managed following general standards-of-care practices aimed at maintaining optimal conditions. Both intraoperative and immediate-postoperative (3-hour) anaesthetic management (unrelated to ventilatory management and FIO_2) will be decided by the attending physician following the established protocols and routines at each centre. However, in order to ensure a high standard of anaesthetic management, a number of common strategies have been established: halogenated agents will be given to maintain anaesthesia,[36] neuromuscular blockade will be monitored and reversed when considered necessary,[37] intra- and postoperative pain will be controlled with neuraxial anaesthetics when indicated,[38] haemodynamic management will be based on advance monitoring, and fluids will be administered following goal-directed therapy principles.[39] Appropriate antibiotic prophylaxis will be administered,[40] glycaemia will be controlled and pharmacological treatment will be adopted to avoid hyperglycaemia,[41] and pharmacological prevention of postoperative nausea and vomiting (PONV) will be implemented.[42] Finally, when nasogastric tube insertion is required, the tube will be withdrawn prior to extubation when possible. All these data will be collected and analysed.[43]

Monitoring

Intraoperative monitoring will include an ECG, pulse oximetry, capnography, glycaemia, bladder or oesophageal temperature measurement, anaesthetic (bispectral analysis; BIS) and neuromuscular blockade (train of four; TOF) depth analysis, invasive blood pressure measurements, and advanced haemodynamics monitoring with minimally invasive techniques (optional depending on the standard clinical practice and availability of equipment at each hospital). The ventilatory parameters monitored by the anaesthesia machine will be: tidal volume (VT), PEEP,

FIO_2, peak airway pressure (P_{aw}), plateau pressure (P_{plat}), driving pressure (P_{plat}–PEEP), and dynamic compliance of the respiratory system (C_{rs}). Postoperative monitoring will include at least an ECG, pulse oximetry and arterial pressure measurements.

General intraoperative ventilator management

Pre-oxygenation prior to induction will be performed for 5 min at an FIO_2 of 0.8 via a tightly sealed face mask. Patients will be ventilated in volume control ventilation (VCV) mode with squared flow, a VT of 8 mL/kg of the predicted body weight (PBW), and a P_{plat} of ≤25 cmH_2O. If the P_{plat} reaches or exceeds 25 cmH_2O, VT will be decreased in 1 mL/kg steps until it drops to ≤25 cmH_2O. Throughout the whole procedure, the respiratory rate (RR) will be set to maintain an end-tidal carbon dioxide partial pressure ($EtCO_2$) of 35–45 mmHg, with an inspiratory to expiratory ratio (I:E) of 1:2 and an inspiratory pause time of 10% of the inspiratory time. During the period of awakening from general anaesthesia (patients with spontaneous ventilation), an FIO_2 of 0.8 will be applied at the same end-expiratory pressure (determined case by case, see subsequent sections), either using PEEP or continuous positive airway pressure (CPAP).

Alveolar recruitment manoeuvre

The ARM is performed after intubation followed by a PEEP-titration trial. Before the ARM is performed, the anaesthesiologist must ensure that there is haemodynamic stability (a mean arterial pressure (MAP) of more than 70 mmHg and/or a cardiac index of more than 2.5 mL/min/m^2) for at least 5 min, a stroke volume variation (SVV) of less than 10%, and an adequate neuromuscular blockade (0 of 4 by TOF). The ARM is performed as follows.

The ventilator is changed from VCV to pressure-controlled ventilation (PCV) with a 20 cmH_2O driving pressure and an RR of 15 breaths per minute (bpm), I:E of 1:1, PEEP of 5 cmH_2O, and maintenance of the randomised FIO_2. For the recruitment phase, the PEEP level is increased in steps of 5 cmH_2O every 10 respiratory cycles, up to a PEEP of 20 cmH_2O to produce an airway opening pressure of 40 cmH_2O which is maintained for 15 respiratory cycles (total manoeuvre time: 180 s). If haemodynamic instability appears during the recruitment phase (a >50% decrease in the cardiac index or MAP), the manoeuvre will be interrupted and 5–15 mg ephedrine or 0.05–0.15 mg phenylephrine will be administered; after haemodynamic stabilisation, a new ARM will be performed. After lung recruitment is accomplished, the optimal PEEP is titrated through a decremental PEEP trial, as described in the following section (figure 2).

Titration of the optimal individual PEEP: decremental PEEP trial

At the end of the last step in the PCV recruitment phase, when the PEEP is 20 cmH_2O, the mode will be switched back to VCV with a VT of 8 mL/kg, RR of 15 bpm and I:E of 1:2. After this, the PEEP is decreased in 2 cmH_2O steps every 30 s until the highest dynamic compliance (C_{dyn}) is observed on the ventilator screen (the point at which C_{dyn} starts decreasing or does not increase any further). Once the best C_{dyn} is ascertained, a new recruitment manoeuvre is performed and the PEEP is adjusted for the best C_{dyn}+2 cmH_2O. In the case of accidental airway depressurisation, a new ARM is performed while an identical PEEP is set (figure 2).

The need for new recruitment manoeuvres and a repeated PEEP trial is evaluated every 40 min by measuring the C_{dyn} and peripheral capillary oxygen saturation (SpO_2). If there is a drop of more than 10% in the C_{rs}, FIO_2 will be transiently decreased to 0.21–0.25 for at least 5 min, and if SpO_2 drops to ≤96% at this FIO_2, a new recruitment and PEEP trial will be performed.

Extubation will not be performed by applying manual positive pressure above the previously set PEEP or CPAP, or while suctioning through the tracheal device. If necessary, aspiration can be performed at least 10 min before extubation. After suction, the patient will be switched

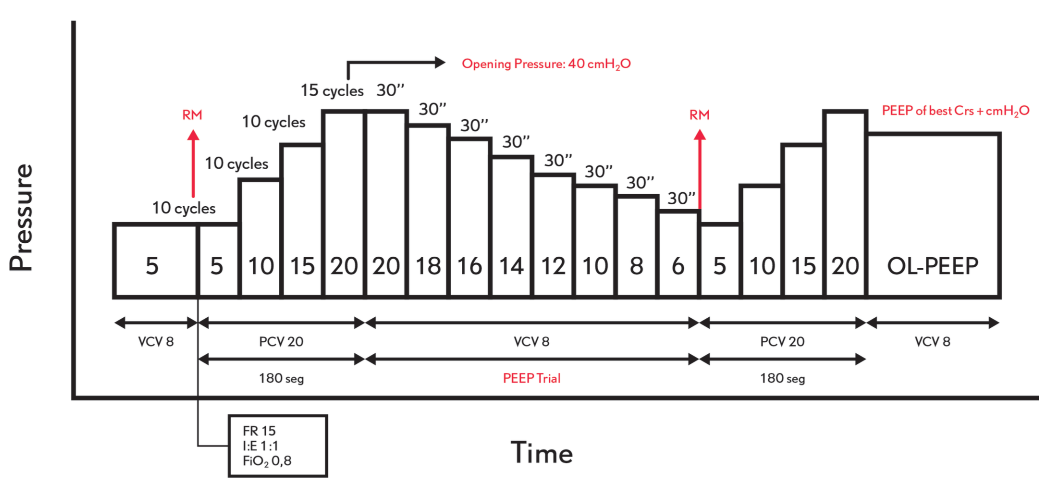

Figure 2 Alveolar recruitment manoeuvre and PEEP titration trial protocol. C_{rs}, respiratory system compliance; I:E, inspiratory-to-expiratory ratio; PEEP, positive end-expiratory pressure; PCV, pressure controlled ventilation; RM, recruitment manoeuvre; RR, respiratory rate; VCV, volume controlled ventilation.

back to mechanical ventilation and a new alveolar recruitment manoeuvre will be performed and the previous PEEP level will be set.

Specific intraoperative ventilatory management

High FIO_2 group

During the intraoperative period, patients will be oxygenated with an FIO_2 of 0.8. Once extubated, patients will maintain the same FIO_2 through non-rebreathing reservoir facemasks with a total flow adjusted to 15 litres per minute (lpm).

Conventional FIO_2 group

During the intraoperative period, patients will be oxygenated with an FIO_2 of 0.3. Once extubated, patients will maintain the same FIO_2 through a Venturi mask with a total flow adjusted to 15 lpm.

Intraoperative rescue manoeuvres

In case of arterial hypoxaemia (SpO_2 ≤92%), after excluding endobronchial tube displacement, bronchospasm, pneumothorax, secretions or a haemodynamic cause, the rescue therapy protocol will be implemented (see sections above). A new recruitment manoeuvre and PEEP trial will then be performed, and if SpO_2 is less than 92%, FIO_2 will be increased in 10% steps until SpO_2 ≥92%.

General postoperative management in the post-anaesthesia care unit

General postoperative management in the post-anaesthesia care unit (PACU) not related to ventilator management and FIO_2 will be decided by the attending physician following the established protocols at each centre. Patients will be oxygenated following extubation with an FIO_2 of 0.3 (conventional FiO_2 group) through a Venturi mask with total flow adjusted to 15 lpm or an FIO_2 of 0.8 (high FiO_2 group) through a non-rebreathing reservoir facemask with a total flow adjusted to 6 lpm for the first 15 min. Arterial oxygenation will be evaluated 15–30 min later when patients are awake and collaborative (Glasgow coma score (GCS) higher than 13), without any residual anaesthetic effect (Richmond scale score of −1 to +1) and pain is under control (verbal analogue pain scale (VAS) score <4), by decreasing the FIO_2 to 0.21 for at least 5 min (Air-Test). The Air-Test is intended to identify possible decreases in SpO_2 related to postoperative atelectasis that may have been masked by the use of supplemental FIO_2; this test will not be performed if the patient already has a SpO_2 below 96% while breathing oxygen at the percentage designated for their study arm. If SpO_2 falls below 96% during the air test, a CPAP of 5 cmH_2O (or 10 cmH_2O if BMI exceeds 30 kg/m^2) will be initiated and maintained for 3 hours, without adjusting the FIO_2 administered according the patient's study arm. If the patient arrives at the PACU or intensive care unit (ICU) still under invasive mechanical ventilation, the above-mentioned management will be applied after extubation.

Postoperative rescue manoeuvre

Rescue therapies will be contemplated whenever SpO_2 decreases to 92% or lower, including during the Air-Test. A positive or negative response will be evaluated in a maximum period of 30 min. During the rescue manoeuvre with CPAP, the patient's randomly assigned FIO_2 will be maintained.

Non-invasive ventilation

The ventilator (specifically for non-invasive ventilation (NIV) or a conventional ventilator with NIV protocol software installed on it) and a NIV interface will be chosen by the attending physician based on the availability of equipment in the hospital. Positive pressure will start with an inspiratory positive airway pressure (IPAP) 5 cmH_2O higher than the expiratory positive airway pressure (EPAP) and will be increased in 5 cmH_2O increments up to 15 cmH_2O. The EPAP will be increased to a maximum of 10 cmH_2O (15 cmH_2O if BMI exceeds 30 kg/m^2). During the rescue manoeuvre with NIV, the FIO_2 will be set according to the centre's general standards-of-care practice and will aim to maintain a SpO_2 ≥92%.

Invasive ventilation

Direct tracheal intubation (without a NIV trial) is indicated if the patient meets at least one of the following criteria:

1. Haemodynamic instability (a systolic blood pressure (SBP) <80 mmHg or <40% of the basal level, or administration of vasoactive drugs for more than 2 hours is required to maintain the SBP above 80 mmHg)
2. Ventricular arrhythmias with haemodynamic instability or ECG signs of myocardial ischaemia
3. A GCS score <9
4. Sedation is required due to agitation.

Tracheal intubation after 1 hour of NIV is indicated in patients meeting at least one of the following criteria:

1. Severe hypoxaemia (SpO_2 <92% while receiving the oxygen concentration randomly assigned to their study arm)
2. Respiratory acidosis (pH <7.30 with a $PaCO_2$ >50 mmHg)
3. Signs of distress with increased use of accessory respiratory muscles or paradoxical thoracic-abdominal respiratory movements.

Study outcome variables

Primary outcome

The primary outcome of the iPROVE-O2 trial is the appearance of SSIs, according to the criteria set out by the Centers for Disease Control (CDC),[44] in study subjects within the first 7 postoperative days.

Secondary outcomes

The secondary outcomes are the composites of all the systemic complications experienced by the subjects in the first 7 postoperative days (points 1–17 below) or in the first 30 postsurgical days (points 1–17 below). The primary and secondary data outcomes will be recorded 3 hours after PACU/ICU admission and at 1, 2, 7 and 30 days after surgery, with a 180- and 365-day follow-up for mortality. Plasma samples will be taken preoperatively and 2 days after surgery. If the patient is not extubated in the operating room, the first four data time points will be taken from the time of extubation.

Secondary outcomes in the first 7 and 30 postoperative days

The the secondary outcomes in the first 7 and 30 postoperative days are as follows:

1. Anastomosis dehiscence: suture-line failure with leakage of the intraluminal contents that may cause peritonitis, fistula from the wound or drain, or appearance of an abdominal fluid collection (diagnosed with imaging) that causes fever, septicaemia or shock[45]
2. Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined as an increase in the sequential organ failure assessment (SOFA) score of 2 points or more[46]
3. Septic shock: sepsis which requires vasopressors to maintain a mean arterial pressure of ≥65 mmHg and serum lactate levels ≥2 mmol/L in the absence of hypovolaemia[46]
4. Requirement for surgical re-intervention
5. PONV[47]
6. Urinary infection[47]
7. Postoperative cognitive dysfunction[47]
8. Paralytic ileus[47]
9. Heart failure[47]
10. Myocardial ischaemia[47]
11. Cardiac arrhythmias[47]
12. Renal failure[47]
13. Pulmonary complications[47]: (i) atelectasis; (ii) mild acute respiratory failure; (iii) severe acute respiratory failure; (iv) ARDS; (v) respiratory infection; (vi) early extubation failure or reintubation requirement; (vii) pleural effusion
14. Infection complication (composite of SSI, pneumonia, urinary infection, sepsis and septic shock)
15. Increased ICU and hospital length of stay (LOS)
16. ICU and hospital readmission in the first 30 postsurgical days
17. Mortality within 30 days
18. Other follow-up variables.

The following baseline variables will be recorded preoperatively: age, sex, height, weight, BMI, American Society of Anesthesiologists (ASA) physical status score, SOFA score, Assessment of Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score,[48] type of intervention and medical history.

Intraoperative parameters (recorded at three different time points: post-induction, 60 min post-induction and pre-extubation) will be: arterial blood gases, SpO_2, FIO_2, respiratory variables (VT, PEEP, P_{aw}, P_{plat}, driving pressure (P_{plat}–PEEP), C_{rs}, respiratory system resistance (R_{aw}), and haemodynamics (PAM, CI), diuresis, glycaemia and temperature. Other relevant data will also be recorded and include: the types of anaesthetic drugs used, type and volume of fluids given, blood loss and transfusion requirements, need for vasoactive drugs, diuresis, nasogastric tube insertion, duration of surgery, mechanical ventilation time, number of recruitment manoeuvres performed, the need for rescue therapy, and the number of patients in each group who become unblinded to their randomisation arm.

Other variables that will be recorded postoperatively are: arterial blood gases, SpO_2, FIO_2, RR, PAM, temperature, glycaemia, SOFA, the National Nosocomial Infections Surveillance System (NNISS) scale score,[49] and wound healing characteristics evaluated using the ASEPSIS (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria and duration of inpatient Stay) score.[50]

Statistical methods

Sample size

The sample size required was estimated based on the literature and our own unpublished data.[35] Assuming that there is a 10% risk of developing an SSI[51] and a relative reduction of 50% in the incidence of these complications in the high FIO_2 open-lung treatment group,[51] using a significance level of 5% and a power of 80%, recruitment of a total of 686 patients (343 in each management group) will be required.[52] This figure was increased to 756 (by adding 10%) to compensate for possible dropouts. The number of patients recruited among centres will be competitive and randomisation will be stratified by hospital in order to ensure a balanced hospital distribution.

Data analysis

Normally distributed variables will be expressed as their mean and SD and non-normally distributed variables will be expressed as their medians and interquartile ranges; categorical variables will be expressed as the sample size number plus percentage (n, %). In test groups of continuous normally distributed variables, the Student t-test will be used; the Mann–Whitney U test will be used for continuous non-normally distributed data. Categorical variables will be compared with the χ^2 test or Fisher's exact test, or when appropriate, as the relative risk. Statistical analysis will be conducted on an intention-to-treat (ITT) basis. Unadjusted χ^2 or Fisher exact tests will be used for primary-outcome analyses. Secondary outcomes will be assessed as the count (total occurrence within the observation window) and binary variables (any occurrence, yes/no).

Given that this is a randomised controlled trial, we expect that the patient baseline characteristics will be sufficiently balanced by the randomisation of this large study population. Nonetheless, baseline balance will be tested, and if an imbalance is discovered, a generalised mixed linear regression model will be used (a Poisson or logistic link, according to type of outcome variable) to (1) take into account any possible confounding covariate adjustments necessary, according to their clinical relevance and (2) to consider within- and between-centre variability. The time-to-event curves will be calculated using the Kaplan–Meier method. Time-to-event variables (primary and secondary outcomes) will be analysed using a proportional hazard model adjusted for possible imbalances in the patient baseline characteristics.

Time-course variables (eg, repeated measurements of vital parameters, blood values, VAS scores, mobility, etc.) will be analysed using a linear mixed-models procedure which expands the generalised linear model (GLM) to expose any otherwise hidden correlations and/or non-constant variability present in the data. The model includes two factors: (1) study group (fixed factor, intervention or control group), where each level of the study group factor can have a different linear effect on the value of the dependent variable; and (2) time as a covariate, where time is considered to be a random sample from a larger population of values, and the effect is not limited to only the chosen times. If the frequency of missing data is >5%, an additional analysis will be performed using the multiple imputation method. A one-sided probability (p) value of less than 0.05 will be considered to indicate statistical significance.

Data management

Personal information will be treated according to the Spanish Personal Data Protection Law (Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal). To optimise the quality of the data, use of an electronic data collection notebook (DCN) will be implemented to automatically cross-check the entries and data-range values. Once all the data are entered into the database, the acceptable error rate for adequate statistical analysis of the database will be less than 0.025% for the primary outcome and less than or equal to 0.6% for the secondary outcomes. Monitoring visits will be performed according to the recruitment rate.

Monitoring plan

The monitoring plan is based on the modified Haybittle–Peto boundaries for stopping trials after interim analyses in the second half of the inclusion period.[53 54] Analysis of the main endpoint will be presented to the data and safety management board with a blinded code for each allocation group. The interim analysis will be conducted when outcome data for 378 trial participants have been obtained. If the interim analysis shows a significant ($p<0.001$) benefit or harm from the intervention, the data and safety management board will advise the steering committee to stop the trial. Should any serious adverse events (SAE) occur during the trial, a specific template has been designed for use in reporting it to the promotor, which will be done within 24 hours of the principal investigator becoming aware of the SAE.

Trial organisation

The steering committee comprises the study's principal investigators who contributed to its design and approved the final protocol. The executive committee comprises the main investigators of each participating centre and is responsible for administrative, trial (the summary of assessments is shown in table 1) and data management. The data and safety management board consists of independent experts in mechanical ventilation and multicentre trials, and recommends the continuance or discontinuation of the study based on the evidence collected at interim analysis intervals. The trial management team comprises a chief investigator, a project manager, a statistician, and an investigator who is an expert in informatics. This team's responsibilities are:

1. Planning and conducting the study: designing the protocol, case report and electronic case report forms (e-CRFs), designing the investigator manual, and managing and controlling the data quality.
2. Research centre support: assisting the centres with the administrative submission, monitoring recruitment rates and taking action to increase recruitment if necessary, monitoring follow-ups, auditing, and sending study material to the research centres.
3. Producing a monthly study newsletter and developing supporting material for the study.
4. Statistical analysis and research reporting: completing the statistical analysis and helping to write the final manuscript.

Table 1 Summary of assessments

	Inclusion (day)	Intraoperative (day 0)	PACU (Day 0)	Day 1, 2, 7, 30	Day 180	Day 365
Eligibility and informed consent	X					
Previous medical history	X	X	X	X		
Demographic data	X					
Treatment/intervention		X	X			
Adverse events		X	X	X	X	X
Perioperative data		X	X			
Postoperative complication			X	X		
ICU/hospital length of stay			X	X		
Mortality		X	X	X	X	X
Protocol deviations		X	X			

ICU, intensive care unit; PACU, post-anaesthesia care unit.

The iPROVE-O2 Network comprises:

Steering committee: Carlos Ferrando, Javier Belda, Marina Soro, Jesus Villar, Jaume Canet, Carmen Unzueta, Fernando Suarez-Sipmann, Gerardo Tusman, Julián Librero, Natividad Pozo and Salvador Peiró.

Statistical committee: Julián Librero and Salvador Peiró.

Executive committee: Carlos Ferrando, Carmen Unzueta, Jaume Canet, Maite Ibáñez, César Aldecoa, Ignacio Garutti, David Pestaña, Aurelio Rodríguez, Santiago García del Valle, Oscar Díaz, Jaume Balust, F. Javier Redondo, Manuel de la Matta, Lucia Gallego, Manuel Granell, Pascual Martínez, Ana Pérez, Sonsoles Leal, Kike Alday, Pablo García, Pablo Monedero and Rafael González Gerardo Aguilar.

Data and safety management board: Berthold Bein, Robert Greif and Emmanuel Futier

Trial management committee: Carlos Ferrando, Natividad Pozo, Marina Soro, Carlos Delgado and Julián Librero.

iPROVE-O2 Network co-investigators: supplementary file

Ethics and dissemination

The iPROVE-O2 study was designed in accordance with the fundamental principles established in the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine and the UNESCO Universal Declaration on the Human Genome and Human Rights, and with the requirements established by Spanish legislation in the field of biomedical research, protection of personal data and bioethics. It was registered on 15 May 2016 at http://www.clinicaltrials.gov with identification no. NCT02776046. Following Spanish legislation, the final protocol was approved by the committee at the reference centre prior to starting patient recruitment. Publication of the results is anticipated in early 2019.

Consent

In accordance with the 2013 Declaration of Helsinki patients will only be included in the trial after they have provided written informed consent.

Dissemination policy

The findings of the trial will be published in peer-reviewed journals and presented at national and international conferences in order to disseminate and explain the research and results. All the investigators will have access to the final data set.

DISCUSSION

This is the first randomised controlled trial designed to specifically evaluate the efficacy of high versus low FIO_2 in preventing SSIs when used as part of an individualised perioperative open-lung ventilatory strategy in patients undergoing abdominal surgery. Physiologically, oxygen transport depends on cardiac output (CO) and arterial oxygen content (CaO_2). With normal CO, haemoglobin (Hb) >10 g/dL and arterial oxygen saturation (SaO_2) ≥97%, increasing the partial pressure of tissue oxygen requires an increased PaO_2. Thus, with adequate tissue perfusion, supplemental FIO_2 is required to increase PaO_2 and the partial pressure of tissue oxygen, as a preventive strategy which favours oxidative killing of pathogens by neutrophils and therefore decreases the rate of SSIs.[12 13]

However, the impact of high compared with conventional FIO_2 in SSI prevention remains uncertain despite numerous randomised controlled trials. Greif et al[16] showed a reduction in SSIs associated with high FIO_2 in 500 patients who underwent colorectal resection. This is also the only trial that has so far measured the partial pressure of tissue oxygen, which was significantly increased with high FIO_2 compared with conventional FIO_2. These results were confirmed by Belda et al[17] in 300 colorectal resection patients, by Bickel *et al* in 210 acute appendectomy patients,[19] and by Schieroma et al[18] in 171 total gastrectomy patients. In all the aforementioned studies, high FIO_2 increased the PaO_2 and this supplemental oxygen reduced the incidence of SSIs and anastomotic dehiscence.

In contrast, Kurz et al[22] did not observe a decrease in SSIs when using high FIO_2 in 586 colorectal resection patients, despite the fact that the PaO_2 was significantly increased in the higher FIO_2 group. Similarly, Meyhoff *et al.* (PROXI trial)[21] found no differences in outcomes between high and conventional FIO_2 in 1400 abdominal surgery patients. Moreover, Pryor et al[23] showed that an increased risk of SSIs was related to high FIO_2 in 165 major abdominal surgery patients. Nevertheless, perhaps these inconsistent results can be explained by the different surgical procedures, inclusion criteria, patient ASA status, length of FIO_2 application, or differing management of factors that are directly related to SSIs such as fluid therapy, pain control, epidural anaesthesia, blood transfusions or glycaemic control.

However, perhaps the main limitation to the adequate interpretation of these inconsistent results is the fact that the ventilatory strategy was not protocolised in any of these trials. This is because the ventilatory strategy is the main factor associated with lung collapse, and therefore also with the relationship between any given PaO_2 values and the corresponding FIO_2 levels. The open-lung strategy reverses lung collapse by using the ARM and prevents the emergence of further collapse by maintaining PEEP. Thus, this strategy maintains the normal lung gas-exchange function during surgery, which increases the PaO_2 and the resulting partial pressure of tissue oxygen for a given FIO_2 percentage.[32–34] In fact, there is wide variation in the PaO_2 found in patients undergoing surgery, depending on whether PEEP, with or without ARM, is applied.[31 32]

This may explain the results from Kurz *et al*[22]: although they found no differences between high and conventional FIO_2, patients with a lower PaO_2 had a higher incidence of SSIs. Moreover, this group also saw a lot of variability between FIO_2 and PaO_2, which they suggest could be explained by the different ventilatory strategies used at the different recruitment centres participating in the study. This shows that the ability of FIO_2 to increase PaO_2 depends on functional lung volume, and therefore also on the ventilatory strategy. Recently, Futier *et al*,[51] using identical FIO_2 between groups, compared an open-lung versus conventional ventilatory strategy in 400 abdominal surgery patients. The open-lung group showed a significantly lower incidence of anastomotic dehiscence and sepsis, and although differences in the SSI rates were not statistically significant, the incidence in the open-lung group was lower compared with the non-protective ventilatory group (10% vs. 15%).

A potential limitation for the use of high FIO_2 is that it may promote absorption atelectasis, which in turn would favour pulmonary shunt and thereby a reduced perioperative PaO_2 and postoperative lung functional impairment. However, these effects can be mitigated by limiting the high FIO_2 to 0.8[55] and by using an adequate level of PEEP.[56] Moreover, Akça *et al*[55] used CT scans to show that there was no difference in postoperative atelectasis between 0.8 and 0.3 FIO_2 in patients undergoing abdominal surgery. Furthermore, Hovaguimian *et al*[26] confirmed these results in their meta-analysis which included randomised controlled trials comparing high to low FIO_2.

Finally, most studies that failed to show any benefit to using high FIO_2 did not measure the PaO_2. In addition, the lack of a protocolised ventilatory strategy may have resulted in some methodological limitations because the efficacy of FIO_2 in increasing and maintaining higher PaO_2 percentages (ie, the tissue PaO_2) in different patients was not measured. In contrast, all of the studies that showed a benefit to using high FiO_2, did measure PaO_2 and found that it significantly differed between the high and low FIO_2 groups. In the clinical trial protocol we describe here, we will evaluate the efficacy of high FIO_2 in preventing SSIs by implementing an individualised global approach to perioperative open-lung ventilation, with the aim of increasing the partial pressure of tissue oxygen. If the trial demonstrates that the high FIO_2 produced using this approach decreases the rates of SSIs, this finding will represent a significant improvement in the management of this surgical population .

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Competing interests The study is an investigator-initiated trial which will be promoted by the Department of Anesthesiology and Critical Care at the Hospital Clínico Universitario in Valencia, Spain.

Patient consent This is a protocol and the trial has not started yet. Each participan will sign a patient consent form before inclusion.

Ethics approval The Ethical Review Board of the Hospital Clínico Universitario of Valencia.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, *et al*. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;372:139–44.
2. Cohen ME, Bilimoria KY, Ko CY, *et al*. Development of an American College of Surgeons National Surgery Quality Improvement Program: morbidity and mortality risk calculator for colorectal surgery. *J Am Coll Surg* 2009;208:1009–16.
3. Michard F, Mountford WK, Krukas MR, *et al*. Potential return on investment for implementation of perioperative goal-directed fluid therapy in major surgery: a nationwide database study. *Perioper Med* 2015;4:11.

4. Khuri SF, Henderson WG, DePalma RG, *et al*. Participants in the VA national surgical quality improvement program. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005;242:326–41.
5. Haley RW, Culver DH, Morgan WM, *et al*. Identifying patients at high risk of surgical wound infection. A simple multivariate index of patient susceptibility and wound contamination. *Am J Epidemiol* 1985;121:206–15.
6. Akça O, Doufas AG, Morioka N, *et al*. Hypercapnia improves tissue oxygenation. *Anesthesiology* 2002;97:801–6.
7. Akça O, Melischek M, Scheck T, *et al*. Postoperative pain and subcutaneous oxygen tension. *Lancet* 1999;354:41–2.
8. Arkiliç CF, Taguchi A, Sharma N, *et al*. Supplemental perioperative fluid administration increases tissue oxygen pressure. *Surgery* 2003;133:49–55.
9. Treschan TA, Taguchi A, Ali SZ, *et al*. The effects of epidural and general anesthesia on tissue oxygenation. *Anesth Analg* 2003;96:1553–7.
10. Fleischmann E, Herbst F, Kugener A, *et al*. Mild hypercapnia increases subcutaneous and colonic oxygen tension in patients given 80% inspired oxygen during abdominal surgery. *Anesthesiology* 2006;104:944–9.
11. Qadan M, Battista C, Gardner SA, *et al*. Oxygen and surgical site infection: a study of underlying immunologic mechanisms. *Anesthesiology* 2010;113:369–77.
12. Allen DB, Maguire JJ, Mahdavian M, *et al*. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* 1997;132:991–6.
13. Chang N, Goodson WH, Gottrup F, *et al*. Direct measurement of wound and tissue oxygen tension in postoperative patients. *Ann Surg* 1983;197:470–8.
14. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. *Arch Surg* 1984;119:199–204.
15. Govinda R, Kasuya Y, Bala E, *et al*. Early postoperative subcutaneous tissue oxygen predicts surgical site infection. *Anesth Analg* 2010;111:1.
16. Greif R, Akça O, Horn EP, *et al*. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000;342:161–7.
17. Belda FJ, Aguilera L, Garcia de la Asuncion J, *et al*. Spanish Reduccion de la Tasa de Infección Quirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA* 2005;294:2035–42.
18. Schietroma M, Cecilia EM, Carlei F, *et al*. Prevention of anastomotic leakage after total gastrectomy with perioperative supplemental oxygen administration: a prospective randomized, double-blind, controlled, single-center trial. *Ann Surg Oncol* 2013;20:1584–90.
19. Bickel A, *et al*. Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis. *Arch Surg* 2011;146:464–70.
20. Myles P, Leslie K, Epi M, *et al and the ENIGMA trial group*. Avoidance of nitrous oxide for patients undergoing major surgery. *Anesthesiology* 2007;107:221–31.
21. Meyhoff CS, Wetterslev J, Jorgensen LN, *et al*. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009;302:1543–50.
22. Kurz A, Fleischmann E, Sessler D, *et al*. Factorial Trial Investigators. Effects of supplemental oxygen and dexamethasone on surgical site infection: a factorial randomised trial. *Br J Anaesth* 2015:1–10.
23. Pryor KO, Fahey TJ, Lien CA, *et al*. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *JAMA* 2004;291:79–87.
24. Wetterslev J, Meyhoff CS, Jørgensen LN, *et al*. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev* 2015:CD008884.
25. Thibon P, Borgey F, Boutreux S, *et al*. Effect of perioperative oxygen supplementation on 30-day surgical site infection rate in abdominal, gynecologic, and breast surgery: the ISO2 randomized controlled trial. *Anesthesiology* 2012;117:504–11.
26. Hovaguimian F, Lysakowski C, Elia N, *et al*. Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2013;119:303–16.
27. Canet J, Belda FJ. Perioperative hyperoxia: the debate is only getting started. *Anesthesiology* 2011;114:1271–3.
28. Strandberg A, Tokics L, Brismar B, *et al*. Atelectasis during anesthesia and in the postoperative period. *Acta Anaesthesiol Scand* 1986;30:154–8.
29. Tusman G, Böhm SH, Warner DO, *et al*. Atelectasis and perioperative pulmonary complications in high-risk patients. *Curr Opin Anaesthesiol* 2012;25:1–10.
30. WHO. Global guidelines on the prevention of surgical site infection. http://www.who.int/gpsc/ssi-guidelines/en/ (accessed 15 Feb 2017).
31. Futier E, Constantin JM, Pelosi P, *et al*. Intraoperative recruitment maneuver reverses detrimental pneumoperitoneum-induced respiratory effects in healthy weight and obese patients undergoing laparoscopy. *Anesthesiology* 2010;113:1310–9.
32. Tusman G, Groisman I, Fiolo FE, *et al*. Noninvasive monitoring of lung recruitment maneuvers in morbidly obese patients: the role of pulse oximetry and volumetric capnography. *Anesth Analg* 2014;118:137–44.
33. Ferrando C, Mugarra A, Gutierrez A, *et al*. Setting individualized positive end-expiratory pressure level with a positive end-expiratory pressure decrement trial after a recruitment maneuver improves oxygenation and lung mechanics during one-lung ventilation. *Anesth Analg* 2014;118:657–65.
34. Maisch S, Reissmann H, Fuellekrug B, *et al*. Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. *Anesth Analg* 2008;106:175–81.
35. Ferrando C, Soro M, Canet J, *et al*. Rationale and study design for an individualized perioperative open lung ventilatory strategy (iPROVE): study protocol for a randomized controlled trial. *Trials* 2015;16:193.
36. Landoni G, Bignami E, Oliviero F, *et al*. Halogenated anaesthetics and cardiac protection in cardiac and non-cardiac anaesthesia. *Ann Card Anaesth* 2009;12:4–9.
37. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg* 2010;111:1–128.
38. Pöpping DM, Elia N, Marret E, *et al*. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg* 2008;143:990–9.
39. Gupta R, Gan TJ. Peri-operative fluid management to enhance recovery. *Anaesthesia* 2016;71 Suppl 1:40–5.
40. Bassetti M, Righi E, Astilean A, *et al*. Antimicrobial prophylaxis in minor and major surgery. *Minerva Anestesiol* 2015;81:76–91.
41. Kotagal M, Symons RG, Hirsch IB, *et al*. For the SCOAP-CERTAIN Collaborative. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. *Ann Surg* 2015;261:97–103.
42. Gan T, Diemunsch P, Habib A, *et al*. Society for Ambulatory Anesthesia. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014;118:85–113.
43. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev* 2007;18:CD004929.
44. Horan TC, Gaynes RP, Martone WJ, *et al*. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol* 1992;13:606–8.
45. Bruce J, Krukowski ZH, Al-Khairy G, *et al*. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg* 2001;88:1157–68.
46. Singer M, Deutschman CS, Seymour CW, *et al*. The Third International Consensus Definitions for Sepsis and Septic shock (Sepsis-3). *JAMA* 2016;315:801–10.
47. 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 Outome (EPCO) definitions. A statement from the ESA-ESCIM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88–105.
48. Canet J, Gallart L, Gomar C, *et al*. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010;113:1338–50.
49. Culver DH, Horan TC, Gaynes RP, *et al*. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med* 1991;91:152S–7.
50. Byrne DJ, Malek MM, Davey PG, *et al*. Post-operative wound scoring. *Biomed Pharmacother* 1989;43:669–73.
51. Futier E, Constantin JM, Paugam-Burtz C, *et al*. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369:428–37.
52. Chow S. *Sample Size calculations in clinical research*: Chapman & Hall/CRC Biostatistics Series, 2008.
53. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44:793–7.

54. Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585–612.
55. Akça O, Podolsky A, Eisenhuber E, *et al*. Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and 2 hours after colon resection. *Anesthesiology* 1999;91:991–8.
56. Edmark L, Östberg E, Scheer H, *et al*. Preserved oxygenation in obese patients receiving protective ventilation during laparoscopic surgery: a randomized controlled study. *Acta Anaesthesiol Scand* 2016;60:26–35.

Rationale and study design for an individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) and its effects on surgical site infection: study protocol for a randomised controlled trial

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Notes