

Intraoperative protective mechanical ventilation in patients requiring emergency abdominal surgery: the multicentre prospective randomised IMPROVE-2 study protocol

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Introduction

Emergency abdominal surgery is associated with a high risk of postoperative complications. One of the most serious is postoperative respiratory failure (PRF), with reported rates up to 20%–30% and attributable 30-day mortality that can exceed 20%. Lung-protective ventilation, especially the use of low tidal volume, may help reducing the risk of lung injury. The role of positive end-expiratory pressure (PEEP) and recruitment manoeuvre (RM) remains however debated. We aim to evaluate whether a strategy aimed at increasing alveolar recruitment by using higher PEEP levels and RM could be more effective at reducing PRF and mortality after emergency abdominal surgery than a strategy aimed at minimising alveolar distension by using lower PEEP levels without RM.

Methods and analysis

The IMPROVE-2 study is a multicentre randomised, parallel-group clinical trial of 680 patients requiring emergency abdominal surgery under general anaesthesia. Patients will be randomly allocated in a 1:1 ratio to receive either low PEEP levels (≤ 5 cm H₂O) without RM or high PEEP levels individually adjusted according to driving pressure in addition to RM, stratified by centre and according to the presence of shock and hypoxaemia at randomisation. The primary endpoint is a composite of PRF and all-cause mortality by day 30 or hospital discharge. Data will be analysed on the intention-to-treat principle and a per-protocol basis.

Ethics and dissemination

IMPROVE-2 trial has been approved by an independent ethics committee for all study centres. Participant recruitment began in February 2021. Results will be submitted for publication in international peer-reviewed journals.

Strengths and limitations of this study

- ⇒ This is a large randomised multicentre trial testing the effect of lung-protective ventilation strategy in emergency abdominal surgery.
- ⇒ The multicentre design, broad inclusion criteria, large sample size and follow-up will support external validity.
- ⇒ The primary endpoint is defined according to well-defined and internationally validated criteria.
- ⇒ Allocation will not be concealed to anaesthesiologists, since they must care patients during surgery; however, study outcomes will be assessor blinded, and data analysis will be performed by a blinded statistician.

INTRODUCTION

Emergency abdominal surgery involves several hundred of thousand people worldwide with reported short-term mortality rate up to 20%.^{1–5} Postoperative pulmonary complications occur frequently in patients undergoing major surgery and are associated with perioperative mortality and morbidity.⁶ Postoperative respiratory failure (PRF), usually defined as failure to wean from mechanical ventilation after surgery or the need for unplanned tracheal reintubation after surgery,^{7 8} is one of the most severe pulmonary complication, with a reported incidence up to 20%–30% after emergency abdominal surgery,^{7 9} and attributable 30-day mortality that can exceed 20%.^{6 7}

Mechanical ventilation is an essential supportive therapy to maintain gas exchange during general anaesthesia, but may contribute to lung injury and postoperative pulmonary complications.¹⁰ Recent guidelines recommend use of lung-protective mechanical ventilation, which comprises the use of low tidal volume (VT) and positive end-expiratory pressure (PEEP), in patients undergoing elective surgery.¹¹ Although it is tempting to suppose that lung-protective ventilation might be beneficial in a broader population, the evidence is lacking. Moreover, although there is increasing evidence supporting the use of low VT ventilation to minimise lung stretch during surgery,¹² there remains significant controversy about the efficacy and safety of high PEEP and recruitment manoeuvres (RMs).¹³ Two randomised clinical trials showed lung-protective ventilation with low VT in addition to high PEEP and RM to prevent against postoperative pulmonary complications when compared with ventilation with high VT plus low PEEP without RM.^{14 15} Two other large randomised trials found no benefit of high PEEP with RM compared with low PEEP without RM in this setting,^{16 17} suggesting that beneficial effects arise primarily from the use of low VT ventilation. Concerns have also been raised about possible negative haemodynamic effects of high PEEP and RMs in these studies.

Conversely, a strategy of low VT ventilation using low PEEP, while minimising alveolar distension, may be insufficient to stabilise alveoli and may promote alveolar derecruitment, thereby increasing the likelihood of ventilator-induced lung injury from atelectrauma.^{18–20} An experimental study showed a strategy of low VT ventilation plus low PEEP without RM to promote higher driving pressure and mechanical power delivered to the respiratory system compared with high PEEP levels with RMs.²¹ As such, this raises the question as to whether this strategy can be applied safely in patients at increased risk of PRF.

The driving pressure, calculated as the difference between plateau pressure (P_{plat}) and PEEP, has been proposed as a means of individualising PEEP setting.¹¹ Data from an individual patient meta-analysis of 17 randomised controlled trials of mechanical ventilation during surgery suggested that increases in PEEP that result in an increase of driving pressure may be associated with increased odds of postoperative pulmonary complications.²² However, to date, data from large randomised clinical trials comparing individualised driving pressure-guided PEEP setting and usual care are lacking.

Objectives

The aim of this study is to compare a strategy aimed at increasing alveolar recruitment by using high PEEP levels individually titrated according to driving pressure and RM with that of a strategy aimed at minimising alveolar distension by using low PEEP levels without RM in patients undergoing emergency abdominal surgery.

Primary objective

To compare the effect of the two ventilation strategies on PRF and mortality in patients receiving low VT lung-protective ventilation during emergency abdominal surgery.

Secondary objectives

To compare the rates of reintubation and use of curative NIV for PRF and the duration of mechanical ventilation between the two ventilation strategies. To compare the rate of postoperative organ dysfunction between the two ventilation strategies.

To compare the duration of intensive care unit (ICU) and hospital length of stay between the two ventilation strategies.

To compare clinical adverse events between the two ventilation strategies.

METHODS AND ANALYSIS

Trial design and setting

The IMPROVE-2 study is an investigator-initiated, prospective, multicentre, randomised, stratified, parallel-group clinical trial with concealed allocation of patients undergoing emergency abdominal surgery 1:1 to a strategy of increased alveolar recruitment, using high PEEP levels individually titrated according to driving pressure and RMs, or a strategy of minimal alveolar distension, using low PEEP levels without RM ([figure 1](#)). The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.²³ The trial will take place at 28 university and non-university centres.

Participant eligibility and consent

All patients admitted to a participating clinical trial site will be considered for participation. Patients will be eligible for randomisation if they fulfil all the inclusion criteria and none of the exclusion criteria ([table 1](#)).

After patient informed consent has been obtained (or proxy consent has been obtained by the patient's next of kin or legally authorised surrogates), study inclusion will be performed immediately before surgery. Because, in emergency situations, obtaining informed consent prior to participation may not be feasible, the study protocol also provides for a waiver of informed consent from the patient's next of kin if he or she is not present at the time of the patient's inclusion. Deferred informed consent will be obtained as soon as possible from participants or legally authorised surrogates for potential continuation of the research

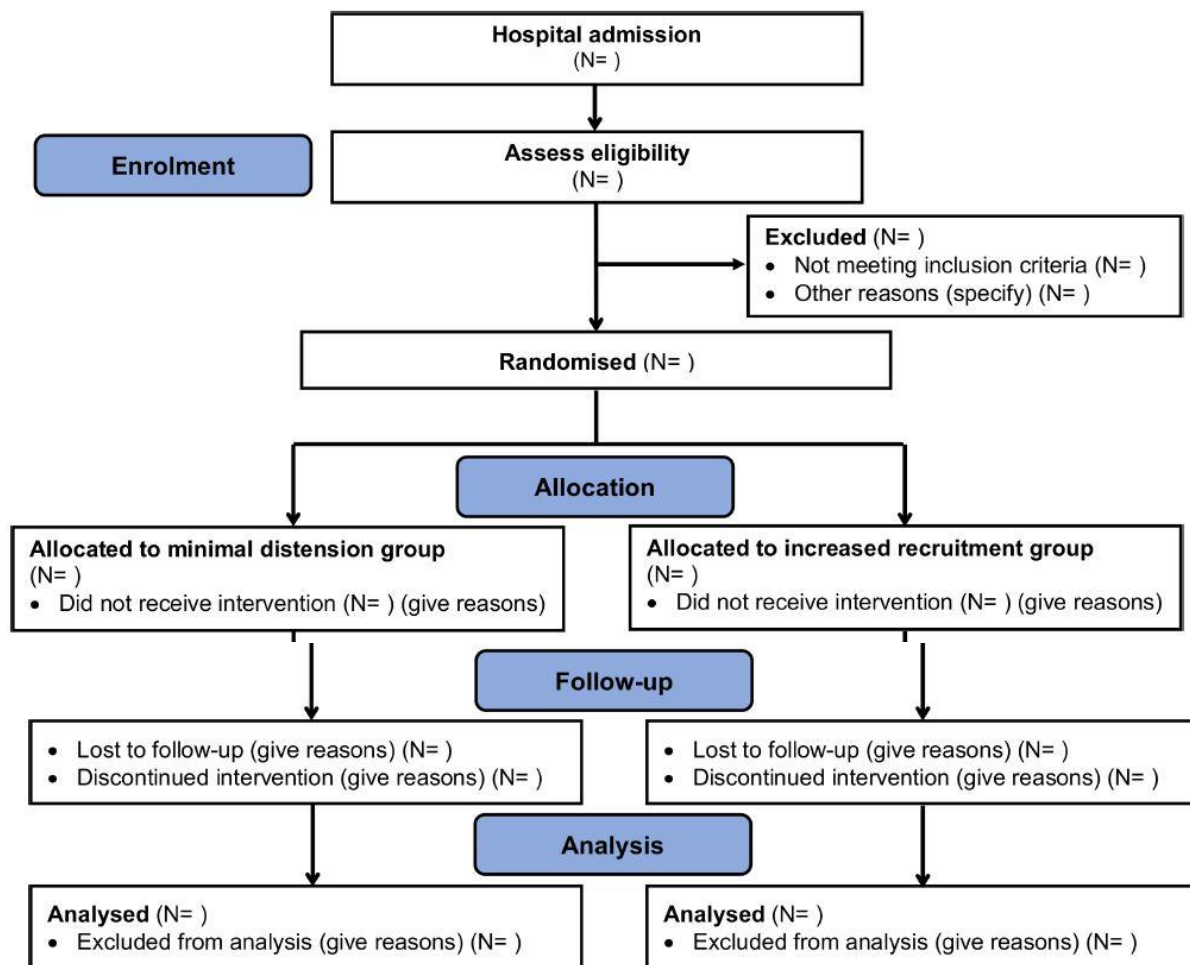


Figure 1 Flow diagram of the IMPROVE-2; Intraoperative Lung Protective Ventilation trial. Flow chart (N=) will be filled during or at the end of the trial.

Randomisation, allocation concealment and blinding Randomisation

Enrolled patients will be randomised by local investigators using a dedicated, password-protected, SSL-encrypted website (CSONline, Clinsight) accessible 24-hour around-the-clock to allow immediate and concealed allocation. Each patient will be given a unique patient-number and a randomisation number. The allocation sequence will be generated in a 1:1 ratio with the use of a minimisation algorithm, stratified according to study centre, the presence or absence of shock (defined by continuous intravenous infusion of vasoactive drugs) and the presence or absence of hypoxaemia (defined by a partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO₂/FiO₂) ratio ≤ 300) at randomisation.

Because arterial blood gas use is declining in emergency department and ICU practice, patients may not have arterial blood gas and arterial partial pressure of oxygen (PaO₂) measurement available in the relevant timeframe. Consequently, non-linear imputation based on the Ellis inversion of the Severinghaus equation will be used to impute PaO₂ from oxyhaemoglobin percent saturation measured with pulse oximetry (SpO₂).²⁴ In patients not on a measured FiO₂, FiO₂ will be estimated by the equation litres of flow/min (up to 15 L) multiplied by 0.03 plus 0.21.²⁵

Inclusion criteria	Exclusion criteria
▶ Adult (18 years or older)	▶ Patients already receiving mechanical ventilation for more than 12 hours before enrolment
▶ Emergency (defined by the need to proceed to surgery within a few hours after diagnosis) surgery	
▶ Laparoscopic or non-laparoscopic abdominal surgery under general anaesthesia	▶ Chronic respiratory disease requiring oxygen therapy or mechanical ventilation at home
▶ Expected duration of 2 hours or more	▶ Undrained pneumothorax or subcutaneous emphysema
	▶ Patients for which death is deemed imminent and inevitable or patients with an underlying disease process with a life expectancy of less than 3 months
	▶ Intracranial hypertension
	▶ Body mass index >40 kg/m ²
	▶ Pregnant or breastfeeding women
	▶ Patients already enrolled in the Intraoperative Lung Protective Ventilation (IMPROVE-2) trial
	▶ Participation in a confounding trial with mortality or postoperative respiratory failure as the main endpoint
	▶ Patient's or relative's refusal to participate
	▶ Guardianship or trusteeship patient
	▶ No affiliation to the social security system

Blinding

Although the allocation group will not be blinded to anaesthesiologists because they have an ethical responsibility to ensure patient safety during surgery, much attention will be given to ensuring strict blinding during the follow-up period and during data collection. At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal, blinded to the allocation group, under the supervision of the local principal investigator or design who will also be unaware of the trial group allocation. Outcome assessors will be blinded to patient anaesthesia records throughout the study. The allocation group will be blinded to the patient, the clinical staff caring for the patient after surgery, the outcome assessors, the data manager and the statistician conducting the analyses until the data will be locked.

Study interventions

Patients eligible for inclusion will be allocated to one of the following two study groups:

▶ Driving-pressure-guided PEEP group (increased alveolar recruitment strategy): external PEEP will be individually set at the highest possible value (up to 15 cm H₂O), providing a driving pressure (airway P_{plat} minus PEEP) lower than 13 cm H₂O,^{22 26} in addition to lung RM. The recruitment procedure will consist in applying a positive airway pressure of at least 30 cm H₂O for 20–30 s¹⁴ after tracheal intubation and repeated every hour and/or in case of disconnection from the ventilator or in case of an increase in driving pressure >13 cm H₂O during surgery.

► Low PEEP group (minimal distension strategy): external PEEP will be set at 5 cm H₂O or lower without RM.[27–29](#)

Minimal distension strategy			Increased recruitment strategy		
Stage	FiO ₂	PEEP level	Stage	FiO ₂	PEEP level
1	Increase FiO ₂ up to 100%	6 cm H ₂ O	1	Do not change FiO ₂	16 cm H ₂ O+repeat recruitment manoeuvre
2	Increase FiO ₂ up to 100%	7 cm H ₂ O	2	Do not change FiO ₂	17 cm H ₂ O+repeat recruitment manoeuvre
3	Increase FiO ₂ up to 100%	8 cm H ₂ O	3	Do not change FiO ₂	18 cm H ₂ O+repeat recruitment manoeuvre
4	Increase FiO ₂ up to 100%	9 cm H ₂ O	4	Do not change FiO ₂	19 cm H ₂ O+repeat recruitment manoeuvre
5	Increase FiO ₂ up to 100%	10 cm H ₂ O (consider applying recruitment manoeuvre)	5	Increase FiO ₂ up to 100%	20 cm H ₂ O+repeat recruitment manoeuvre (consider increasing FiO ₂)

FiO₂, fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure.

In each group, patients will receive volume-controlled low VT ventilation, with a VT of 6–8 mL/kg predicted body weight, calculated according to a predefined formula: $50+0.91(\text{centimetres of height} - 152.4)$ for males and $45.5+0.91 \times (\text{centimetres of height} - 152.4)$ for females. The respiratory rate will be adjusted to maintain end-tidal partial pressure of CO₂ between 35 and 45 mm Hg, with an inspiratory-to-expiratory time ratio of 1:2, an end-inspiratory pause of 30%, and an FiO₂ adjusted to maintain SpO₂ $\geq 94\%$. The maximum limit for respiratory rate is defined by the recognition of auto-positive end expiratory pressure, defined as an expiratory flow that does not return to zero before the next inspiration on the expiratory portion of the flow waveform. In addition, a P_{plat} of no more than 28 cm H₂O will be targeted. If the P_{plat} reaches or exceeds 28 cm H₂O, VT will be decreased by 1 mL/kg followed, in case of insufficiency, by a 1 cm H₂O decrease of PEEP, and so on, until P_{plat} drops below 28 cm H₂O. If the end-tidal partial pressure of CO₂ target is not achieved, and the maximum limit for respiratory rate is reached, VT will be increased up to 8 mL/kg predicted body weight unless P_{plat} is 28 cm H₂O. If patients meet criteria for denoting refractory acidosis (pH ≤ 7.10), anaesthesiologists caring for the patient will, at their discretion, deviate from the assigned ventilation strategy and stop the intervention. In each group, in case of oxyhaemoglobin desaturation, defined as SpO₂ $\leq 92\%$ for more than 5 min, a rescue strategy is provided ([table 2](#)). In each group, the allocated mechanical ventilation strategy will be maintained until the end of surgery. Immediate interruption of sedation will be encouraged after the end of surgery and weaning from the ventilator will be initiated as soon as possible, using previously defined criteria.[30](#) The decision to stop sedation and to initiate weaning from the ventilator will be made by the clinical staff caring for the patient after surgery. Decisions about all other aspects of patient care during the intraoperative and postoperative periods, including the requirement of invasive mechanical ventilation for reoperation or other procedures under general anaesthesia, will be decided following usual practice and the expertise of the staff of the involved centres to minimise interference with the

trial intervention. Trial investigators will be strongly encouraged to manage postoperative analgesia using a multimodal approach targeting numeric rating scale pain scores <3 (or Behavioural Pain Scale score <5).³⁰

Outcome measures

Details on trial endpoints definitions are given in online supplemental file 1.

Primary outcome measure

The primary outcome is a composite of PRF, as defined previously as failure to wean from the ventilator after surgery or requiring unplanned reintubation or curative non-invasive ventilation once extubated postoperatively,^{7 8} and all-cause mortality by day 30 or hospital discharge.

Secondary outcome measures

▶ Key secondary endpoints

- PRF within 30 days following randomisation.
- All-cause mortality within 30 days following randomisation.

▶ Secondary efficacy endpoints

- Severity of postoperative pulmonary complications within 30 days following surgery. Pulmonary complications will be scored on a grade scale ranging from 0 to 4, with grade 0 representing the absence of any pulmonary complication and grades 1–4 representing successively the worse forms of pulmonary complications, as defined previously.³¹

- Sepsis and septic shock within 30 days following surgery.
- Renal dysfunction (defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 1 or higher within 30 days following surgery).
- Sequential (sepsis-related) Organ Failure Assessment (SOFA, modified from³² score from postoperative day 1 to day 7.
- Ventilator-free days (VFDs) to 30 days. A VFD is defined as the receipt as <2 hours of invasive mechanical ventilation or non-invasive mechanical ventilation (as curative therapy) within a 24-hour period.
- Duration of mechanical ventilation from randomisation to first tracheal extubation.
- Total duration of mechanical ventilation (additive, for all episodes up to 30 days after surgery).
- Time to successful tracheal extubation (defined as absence of ventilatory support during the first 48 hours after extubation).³³
- ICU-free days (censored at 30 days following surgery).

– Duration of ICU and hospital stay (patients who will be outside the hospital but in other types of healthcare facilities at day 30 will be considered to have been discharged home).

– Time to death (or censoring).

Tertiary outcome measures

- ▶ Postoperative hypoxaemia, as defined previously.[34](#)
- ▶ Postoperative pneumonia, defined according to consensus guidelines.[8 35](#)
- ▶ Acute respiratory distress syndrome (ARDS), defined according to the Berlin criteria.[36](#)
- ▶ Amount of intravenous fluids (crystalloids and colloids) during surgery.
- ▶ Amount of vasopressor (norepinephrine, phenylephrine, ephedrine) during surgery.
- ▶ Mechanical power calculated as proposed previously. [37 38](#)
- ▶ Ventilatory-related adverse events: haemodynamic instability (defined as a drop of arterial systolic pressure below 80 mm Hg for more than 5 min not responding to intravenous fluids and/or vasopressors), pneumothorax.
- ▶ Rescue therapy for hypoxaemia.
- ▶ All-cause mortality to day 90.

Statistics

Sample size estimation

Assuming a 10% mortality rate[6](#) and a 15% rate of PRF 30 days after surgery[7 9](#) (thus 25% for the composite endpoint), 2×340 patients will be needed to have 90% power to show an absolute between-group difference of 10% in the primary outcome measure at a two-sided alpha level of 0.05.

Statistical analysis

All analyses will be performed with the use of Stata software (V.15, StataCorp) before the breaking of the randomisation code, in line with the International Conference on Harmonisation Good Clinical Practice guidelines. Analyses are detailed in a separate statistical analysis plan (see online supplemental file 2).

Data registration

Data are collected and entered into a web-based eCRF (CSOnline, Clinsight) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF, the trial database will be established. Paper case report form will be

used in case of technical difficulties with the eCRF. Data collection will be monitored by trained research coordinators. The following data will be registered:

Prerandomisation and baseline characteristics

Date and time of hospital admission, and source of admission (emergency department, surgical ward, ICU); demographic data (age, sex, weight, height, body mass index); American Society of Anesthesiologist physical status; comorbidities (arterial hypertension: Y/N, diabetes: Y/N, active smoking: Y/N, alcohol abuse: Y/N, chronic pulmonary disease: Y/N, cancer: Y/N); reoperation procedure: Y/N (if Y, date and time of previous surgical intervention); results of blood samples (standard lab. values for white cell count, haemoglobin, platelets, lactate, C reactive protein, bilirubin, creatinine); values for SOFA scoring, date and time of preoperative initiation of mechanical ventilation, if any; indication for emergency

At randomisation (• } 1 hour)

Vasopressor use: Y/N (stratification variable); hypoxaemia (PaO₂/FiO₂ <300): Y/N (stratification variable); haemodynamic variables: heart rate (beats/min), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), mean arterial pressure (mm Hg); oxyhaemoglobin percent saturation (SpO₂) and FiO₂ (or litres of oxygen flow/min and estimated FiO₂).

Intraoperative data

Date and time of admission in the operating room; type of surgery; type of surgical procedure (laparoscopic: Y/N, non-laparoscopic: Y/N); type of anaesthesia (epidural analgesia: Y/N, inhaled anaesthetic: Y/N, intravenous anaesthetic: Y/N, nitrous oxide: Y/N); type (sufentanil: Y/N, remifentanil: Y/N, other) and total dose of opioids; duration of anaesthesia (minutes) from the start of anaesthesia until discharge from the operating room; duration of surgery (minutes) from the start of skin incision until the end of skin closure; type (crystalloids and colloids) and volume (millilitres) of intraoperative fluids; vasopressor use: Y/N (receipt of norepinephrine, epinephrine, phenylephrine, ephedrine) and dose; inotrope use: Y/N (receipt of dobutamine, dopamine); haemodynamic (stroke volume and/or cardiac output) monitoring: Y/N; blood losses (millilitre) and volume of transfused blood (number of unit); ventilator settings after tracheal intubation and, then, hourly until after abdominal closure, and adjustments if any: VT (ml/kg PBW), PEEP (cm H₂O), FiO₂, peak pressure (cm H₂O), Pplat (cm H₂O), RM: Y/N (and number of manoeuvres); ventilator-related adverse events: Y/N (including haemodynamic instability, defined as a drop in systolic arterial pressure below 80 mm Hg for more than 5 min not responding to fluids and/or vasopressors, pneumothorax and any other life-threatening reason for which the clinician would decide to stop the intervention)

On postoperative day 1 (12 hours after surgery)

Patient location (ICU: Y/N, HDU: Y/N, surgical ward: Y/N); presence of invasive mechanical ventilation: Y/N (if yes, ventilation mode, VT, PEEP, FiO₂, peak pressure, Pplat); sedation interruption: Y/N (if yes, date and time of sedation interruption); successful weaning test: Y/N (if yes, date and time of the first weaning test); failure to wean from the ventilator: Y/N; tracheal extubation: Y/N (if yes, date and time of tracheal extubation); oxygen therapy: Y/N (if yes, litres of oxygen flow/min); ventilatory support after extubation: Y/N (if yes, high-flow

Nasal cannula: Y/N, preventive NIV : Y/N); results of arterial blood gases (standard lab. values, when available, for PaO₂, PaCO₂, pH); values for Simplified Acute Physiology Score II and SOFA scoring; reintubation: Y/N (if yes, date, time and reason of reintubation); curative NIV: Y/N (if yes, date and time of initiation); survival status (date and time of death is any).

Daily (08:00 hour) from postoperative day 2 until ICU/High- Dependency Unit (HDU) discharge

Patient location (ICU: Y/N, HDU: Y/N); presence of invasive mechanical ventilation: Y/N (if yes, ventilation mode, VT, PEEP, FiO₂, peak pressure, Pplat); sedation interruption (if still mechanically ventilated the day before): Y/N (if yes, date and time of sedation interruption); successful weaning test (if still mechanically ventilated the day before: Y/N (if yes, date and time of the weaning test); tracheal extubation (if still mechanically ventilated the day before): Y/N (if yes, date and time of tracheal extubation); oxygen therapy: Y/N (if yes, litres of oxygen flow/min); ventilatory support: Y/N; (if yes, high-flow nasal cannula: Y/N, preventive NIV: Y/N); reintubation: Y/N; (if yes, date, time and reason of reintubation); curative NIV: Y/N (if yes, date and time of initiation); values for SOFA scoring (until day 7 following surgery); postoperative pulmonary complications: Y/N (if yes, postoperative pulmonary complication grade (from 1 to 4), hypoxaemia: Y/N, pneumonia: Y/N, ARDS: Y/N); postoperative non-pulmonary complications: Y/N (if yes, sepsis/septic shock: Y/N, renal dysfunction (KDIGO score): Y/N, other: Y/N); discharge from ICU/HDU: Y/N (if yes, date and time of discharge); discharge from hospital: Y/N (if yes, date and time of discharge); survival status (date and time of death is any)

Thirty days after randomisation (or hospital discharge)

Discharge from hospital: Y/N (if yes, date and time of discharge); discharge from ICU/HDU: Y/N (if yes, date and time of discharge); New ICU/HDU admission (in case of discharge from ICU/HDU before day 30): Y/N (if yes, date and time of admission); presence of invasive mechanical ventilation: Y/N; duration (days) of invasive mechanical ventilation from randomisation to first tracheal extubation following surgery; duration (days) of invasive mechanical ventilation from randomisation (additive, for all episodes up to 30 days after surgery); duration of NIV (additive, up to 30 days after surgery); VFDs to day 30; postoperative pulmonary complications: Y/N (if yes, hypoxaemia: Y/N, pneumonia: Y/N, ARDS: Y/N); postoperative non-pulmonary complications: Y/N (if yes, sepsis/septic shock: Y/N, renal dysfunction (KDIGO score): Y/N); length of stay (and date of discharge) in ICU/HDU/surgical ward; survival status (and date of death).

Ninety days after randomisation

Survival status (and date of death).

Study discontinuation and patient withdrawal

A participant or a patient's relative who no longer agrees to participate in the clinical trial may withdraw its consent at any time without need of further explanation. In order to conduct intention-to-treat analyses with as little missing data as possible, it is in the interest of the trial to collect as much data from each participant as possible. In accordance with the French law, data already collected prior and up to the date of consent withdrawal will be retained and

analysed. If data for the primary endpoint are not yet available, the investigator may ask the participant and/ or relatives, whenever possible, for permission to obtain data for the primary outcome measure. If this person declines, all data from that patient will be destroyed and a new patient will be randomised to obtain the full sample size. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Ethics and dissemination

The IMPROVE-2 trial is an investigator-initiated trial funded by the French Ministry of Health obtained in 2016 from a national hospital clinical research programme

(Programme Hospitalier de Recherche Clinique National 2016).

The study protocol and statistical analysis plan have approved for all centres from a central ethics committee (Comité de Protection des Personnes Sud-Est III, Bron, France; Registration No. 2019-009B). The trial is registered in the European Clinical Trials Database (EudraCT No. 2019-A00265-52).

A scientific committee, including EF, SJ and TG conceived, drafted and wrote the project.

A data monitoring and safety committee (DMSC) will review unblinded data and serious adverse events at $n=170$ and $n=340$ to advise on any recruitment and safety issues they identify and to investigate whether the conduct of the trial may compromise patient safety (a between-group difference in mortality). Recommendations for pausing or stopping the study will be made by the DMSC if the p value is less than 0.00001 (first interim analysis) or less than 0.003 (second interim analysis) for the between-group difference in the incidence of mortality (O'Brien-Fleming spending function).

Trial results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users.

Data handling and retention

Data will be entered into a web-based eCRF by trial personnel. Each site will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data. Data will be handled according to the French law. All original records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final data set.

Trial status

The current protocol is version 5.0. The trial began on the 18 February 2021. At the time of manuscript submission, 170 patients had been recruited, with a 2-year recruitment period per study site planned.

Data statement

The data generated and/or analysed during the trial are not yet publicly available as the trial is ongoing. When the trial is complete, data sets will be available from the principal investigator (EF) on reasonable request and after agreement by ethics (see online supplemental file 3).

Patient and public involvement

There is no patient and public involvement in the design and execution of this study.

DISCUSSION

The IMPROVE-2 trial is to allow us to evaluate whether a ventilation strategy of increased alveolar recruitment delivered to patients undergoing emergency abdominal surgery is associated with a significantly lower incidence of PRF and death. Postoperative pulmonary complications, and even more PRF, are a particularly significant problem following emergency surgery and affect several thousands of patients worldwide each year. The prevention of postoperative pulmonary complications has been identified one of the top ten current priorities in perioperative intensive care medicine.³⁹ Mechanical ventilation is among the modifiable risk factors associated with the development of postoperative pulmonary complications. However, although some guidelines have been issued, providing evidence-based recommendations for the settings of mechanical ventilation during elective surgery,¹¹ there remains significant controversy about the effects of PEEP and RM and a gap in knowledge in the context of emergency surgery.

Among the strengths of the trial are the multicentre design and the use of a robust primary endpoint that is pertinent to this high-risk patient population. The composite primary endpoint in the IMPROVE-2 trial consists in two components (PRF and all-cause mortality by day 30 or hospital discharge). Combined, these components may provide a clinically meaningful measure of efficacy in improving outcome after mechanical ventilation. Additionally, the patient group is easily identified in daily clinical practice combined with limited exclusion criteria lessening the chance of selection bias.

One limitation of the study is that anaesthesiologists are aware of the inclusion group and the patient anaesthesia record may be accessible to the clinical staff caring for the patient after surgery. However, given the characteristics of the two ventilation strategies under evaluation, a double-blind trial is not possible. The IMPROVE-2 trial, however, aims at minimising detection bias by blinding of the outcome assessor. Additionally, adjustments will be made after multivariate logistic regression by including variables independently associated with the primary outcome, and anticipated relationship with PRF. Finally, the study is not aimed at collecting data on all potential covariates (including blood products other than red blood cells) that may influence the association between the intervention and postoperative outcome

measures. However, stratified random allocation of patients to study groups will help minimise potential confounding.

In conclusion, the IMPROVE-2 trial is an investigator-initiated pragmatic randomised clinical trial empowered to test the hypothesis that a lung-protective ventilation strategy aimed at increasing alveolar recruitment, using RM and driving pressure-guided individualised high PEEP levels, in comparison to a lung-protective ventilation strategy aimed at limiting alveolar distension, would help at reducing PRF and death after emergency surgery. Emergency abdominal surgery is common and optimisation of the mechanical ventilation strategy holds a markedly clinical potential to improve outcome.

Contributors

EF, TG, KA, GC and SJ are members of IMPROVE-2 trial scientific committee, and contributed to the conception and design of the research protocol. EF and BP designed the statistical analysis plan. LK, EF, TG, LA, JB and SJ contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. EF, TG, SJ and BP critically revised the protocol for intellectual content and approved the final version to be published.

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Disclaimer

The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

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