Title: Rationale and study design for an **I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy: study protocol for a prospective international randomized controlled trial.

Short Title: iPROVE-EAL

Protocol version: IPROVE-EAL. Version 03.0 data: 11-february 2020

Sponsor: Department of Anesthesiology and Critical Care, Hospital Clinic de Barcelona.

Protocol registration numbers:

Clinicaltrials.gov identifier: NCT04229810
Ethics Committee number: HCB/2020/0030

1. General Information

1.1 Title: Rationale and study design for an **I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy: study protocol for a prospective international randomized controlled trial.

1.2 Acronym: iPROVE-EAL

1.3 Protocol version: 03.0 **Version Date:** 11-02/2020

1.4 Study Sponsor:
Anesthesiology and Critical Care Department.
Hospital Clinic de Barcelona
C/Villarroel, 170. Barcelona. 08036

1.5 Coordinating investigator:
Carlos Ferrando, MD, PhD
Dept. of Anesthesiology and Critical Care
Anesthesiology and Critical Care Department.
Hospital Clinic de Barcelona
C/Villarroel, 170. Barcelona. 08036
Email: cmferrando@clinic.cat
Tel: +34 609 892 732

1.6 Study Methodology:
Julian Librero, MD, PhD
Navarrabiomed, Complejo Hospitalario de Navarra,
UPNA, REDISSEC (Red de Investigación en Servicios de Salud)
Email: julian.librero@gmail.com

1.7 Coordinating and Study monitoring:
Felix Wantang
Dept. of Anesthesiology and Critical Care
Anesthesiology and Critical Care Department.
Hospital Clinic de Barcelona
C/Villarroel, 170. Barcelona. 08036
Email: darriba@clinic.cat

1.8 Steering Committee:

Guillermo Laguna[1], Fernando Suárez-Sipmann[2,3], Gerardo Tusman[4], Javier Ripollés[5], Oscar Díaz-Cambronero[6], Roger Pujol[1], Eva Rivas[1], Ignacio Garutti[7], Ricard Mellado[1], Jordi Vallverdú[1], Adriana Jacas[1], Julián Librero[8], Jesús Villar[3,9], Carlos Ferrando[3,10]

1. Department of Anesthesia and Critical Care, Hospital Clínic, Barcelona, Spain.
2. Intensive Care Unit, Hospital Universitario, Madrid, Spain.
3. CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.
4. Department of Anesthesia, Hospital Privado de Comunidad, Mar de Plata, Argentina.
5. Department of Anesthesia, Hospital Infanta Leonor de Madrid, Spain.
6. Department of Anesthesia, Hospital La Fe de Valencia, Spain.
7. Department of Anesthesia, Hospital Universitario Gregorio Marañón, Madrid, Spain.
8. Navarrabiomed-Fundación Miguel Servet, Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain.
9. Multidisciplinary Organ Dysfunction Evaluation Research Network, Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain.
10. Department of Anesthesia and Critical Care, Hospital Clínic, Institut D'investigació August Pi i Sunyer, Barcelona, Spain

1.9 Scientific Committee:

Carlos Ferrando, Jesús Villar, Gerardo Tusman, Fernando Suárez-Sipmann

1.10 Data monitoring and safety committee (DMSC):

The DMSC will be composed of clinicians and a biostatistician that, collectively, have experience in the management of surgical patients, have specific expertise in mechanical ventilation, and in the conduct, monitoring and analysis of randomized clinical trials.

The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about

stopping or continuing the trial to the Steering Committee (SC) of the iPROVE-EAL. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.
The committee consists of: to be determined

1.11 Clinical Research Ethical Committee:
The ethical committee approved the protocol version 03.0 with code HCB/2020/0030 on 21/05/2020 (appendix 1).

1.12 Spanish Agency of Drugs and Medical Devices (AEMPS):
The study was classified by the AEMPS as "Estudio no observacional sin medicamentos" (Appendix 2).

1.13 Participating Centers and Local Principal Investigators:
iPROVE research network: centers that have participated in the iPROVE, iPROVE-O2 and iPROVE-OLV trials will be invited to participate. The study will be open for new centers.

1.14 Estimated trial timeline

Within the study the following phases can be distinguished, some of which are already initiated.
Protocol drafting and dissemination at international level for the inclusion of centers.
• Drafting and closing of the protocol by the Scientific Committee of the study together with the statistician during the first quarter of 2020.
• Following the drafting of the protocol, during the second quarter of 2023, the dissemination will be carried out by means of an invitation letter to the iPROVE Network researchers.
Registration of the study, classification of the AEMPS and approval of the EC.
• Once the protocol is closed, during the fourth second of 2020 the study will be registered in clinicaltrials.gov, request the classification of the AEMPS and process the authorization of the reference EC at the Hospital Clínic de Barcelona. This will be done by Dr. Ferrando.
Inclusion of patients and data collection.
• This stage will begin in each center after the approval of each local EC from the first quarter of 2024
• It is estimated a duration of inclusion of patients and data collection of 26 months from the recruitment of the first patient in the study
Final analysis of the data.

During the first quarter of the 3rd year, and following what is described in the "Study Design" section, the clinical epidemiologist, in collaboration with the project manager and the IPs, will perform the final analyzes.

Manuscript Drafting

The drafting of manuscripts will begin during the 2nd quarter of the 3rd year. All members of the research team and the other participating researchers will be authors of the publications generated by this study. Successive drafts will be distributed among all of them to collect their contributions and corrections.

2 Study summary

Background

Postoperative pulmonary complications (PPCs) are the most frequent postoperative complications, with a significant impact on the morbidity, mortality and consumption of health system resources. It has been observed that the incidence of PPCs in this population is between 20% described in observational cohort studies up to 40% in randomized clinical trials. However, the incidence of PPCs in patients undergoing emergency abdominal surgery is not well defined. The lung protective ventilation strategy aims to minimize lung injury favored by mechanical ventilation and therefore to reduce PPCs.

The open lung strategy (OLA), which until now has been defined as a strategy that combines RM to open the alveolar collapse followed by a PEEP level to prevent re-collapse, aims to homogenize the lung decreasing the risk of lung injury and therefore the appearance of PPCs. However, the literature is inconclusive in the benefits that this strategy has over PPCs.

Objectives

A randomized clinical trial that compares an individualized and monitored perioperative open lung ventilation strategy versus a conventional standardized lung protective ventilation in patients undergoing emergency abdominal surgery with clinical signs of lung collapse.

Design

Multicenter, international, parallel-group, open-label, centrally randomized, stratified, clinical trial.

Inclusion and exclusion criteria:

Inclusion criteria: The study population consists of adult men and women ≥18 years of age who underwent emergency abdominal surgery and sign the informed consent, with the presence of post-induction positive air-test (SpO_2 <97% after a maximum of 15 minutes at FIO_2 of 0.21). A SpO_2 <97% at any FIO_2 would also be considered a positive

air-test. Exclusion criteria: 1) Pregnancy or breast feeding, 2) Moderate or severe ARDS defined, 3) refractory shock, 4) diagnosis or suspected intracranial hypertension (>15mmHg), 5) mechanical ventilation in the last 15 days (including CPAP), 6) presence of pneumothorax or giant bullae in a chest radiograph or computed tomography (CT), 7) patients participating in another intervention study with the same or similar primary outcome variable.

Experimental intervention

Intra and postoperative open lung approach, including recruitment maneuvers, individualized PEEP and individualized postoperative respiratory support (PRS)

Control intervention

Standard intraoperative lung protective ventilation plus postoperative low flox oxygen therapy.

Primary Outcomes

Postoperative pulmonary complications during the first 7 postoperative days, including: 1) Acute respiratory failure, 2) Pneumothorax, 3) Weaning failure, 4) Acute respiratory distress syndrome (ARDS), 5) Pulmonary infection.

Sample size

The calculation of the sample size for the main objective was done assuming a 95% confidence level, a percentage of pulmonary complications of 35% at 7 days post-intervention and to be able to detect as significant an absolute reduction of 10% in the incidence of pulmonary complications. Assuming 5% of possible losses, the final sample size is 732 patients (366 per group). The sample size calculation will be readjusted during the pre-planned interim analysis with the data obtained in a preliminary observational study PEAL project and the results obtained in the intermediate analysis of the study (iPROVE-EAL project).

3 List of abbreviations

AEMPS: Spanish agency of drugs and medical devices
ARDS: acute respiratory distress syndrome
ASA: American Society of Anesthesiology physical Status
Cdyn: Dynamic respiratory system compliance
CGS: Coma Glasgow scale
CPAP: Continuous positive airway pressure
CRF: case report form
CT: Computed tomography
DMSC: Data monitoring and safety committee
DP: Driving pressure
EC: Ethical Committee
ECG: electrocardiogram

EtCO2: end-tidal carbon dioxide
FiO2: Inspiratory oxygen fraction
GCP: Good clinical practice
IC: cardiac index
ICU: Intensive Care Unit
iHFNC: Individualized High flow nasal cannula
iOLA: Individualized open lung approach
IOT: oro-tracheal intubation
LUS: Lung ultrasound
MAP: mean arterial pressure
NIV: non-invasive ventilation
O2: Oxygen
PaO2/FiO2: Partial pressure of arterial oxygen to inspiratory oxygen ratio
PaCO2: Arterial partial pressure of carbon dioxide
PACU: Post-anesthetic care unit
Paw: Peak airway pressure
PCV: Pressure controlled ventilation
PEEP: Positive end-expiratory pressure
PPCs: Postoperative pulmonary complications
Raw: Respiratory system resistance
RM: Recruitment maneuvers
RR: Respiratory rate
SAE: Severe Adverse Event
SBP: systolic blood pressure
SOFA: Sequential organ failure assessment
SpO2: Peripherical oxyhemoglobin saturation
STROBE: strengthening the reporting of observational studies in epidemiology
STD: Standard
TOF: train of four
VAS: Visual analogue score
VCV: Volume controlled ventilation
VT: Tidal volume

4 Background (Current State of Scientific knowledge)

Postoperative pulmonary complications (PPCs) are the most frequent postoperative complications, with a significant impact on the morbidity, mortality and consumption of health system resources.[1-3] In recent years there have been numerous publications describing perioperative factors related to these, with the objective of defining the risk of onset and trying to establish prevention strategies,[4,5] as well as clinical studies comparing different lung protection strategies to reduce their appearance.[6-9] Within these, our groups in Spain (iPROVE Research Network group and REDGERM) has lead in the last 5 years three multicenter randomized controlled trials (NCT02158923, NCT02776046, NCT03182062) and 7 multicenter observational (NCT03012802,

NCT03570944, NCT03864861, NCT03865810, NCT03814681, NCT03803280, NCT04305314) studies that has generated so far 13 publications in high impact international journals.

One of the most studied populations are patients undergoing scheduled abdominal surgery, a population that, according to the different risk scales, is considered a moderate to severe risk patient suffering from PPCs. It has been observed that the incidence of PPCs in this population is between 20% described in observational cohort studies up to 40% in randomized clinical trials.[7-9] However, the incidence of PPCs in patients undergoing emergency abdominal surgery is not well defined. Different studies such as ARISCAT or LAS VEGAS have shown that emergency abdominal surgery is an independent risk factor for PPCs.[4,5] Recently, Watson et al. described an incidence of 48% in 568 patients included in the British national audit of emergency laparotomy (NELA).[10,11] If this number of PPCs is extrapolated to Spain, where approximately 140,000 emergency abdominal surgeries are performed per year[12], it means that 70,000 patients per year will suffer at least one PPC. With an average cost of 2,800 euros per lung complication, the minimum impact on the public health system is close to 200 million euros / year.[13,14]

To date there is no further data on the real prevalence in Spain and the factors related to its occurrence, as well as randomized clinical trials studying ventilatory strategies to reduce PPCs in this population. Watson et al. in the aforementioned prospective observational study showed interesting data, such as the protective ventilation strategy defined by the authors as a combination of low tidal volume (VT), recruitment maneuvers (RM) and positive end-expiratory pressure (PEEP) > 5 cmH_2O is applied to less than 5% of patients. Among the registered variables related to ventilatory management, it was shown that peak pressure and inspiratory oxygen fraction (FIO_2) were associated with an increased risk of suffering PPCs.[10] However, other variables that have shown an association with PPCs, such as the plateau pressure or the driving pressure (DP) were not recorded.[15] On the other hand, unlike what has been described in various clinical trials and meta-analysis that have demonstrated a protective effect of RM and PEEP (among which are our studies),[1,8-9,16] in the analysis of Watson et al., these were not related to PPCs. Although the recruitment maneuvers were only performed in 54 (9.5%) patients and the study did not specify how PEEP was adjusted.

The lung protective ventilation strategy aims to minimize lung injury favored by mechanical ventilation, trying to avoid its two main mechanisms: tidal overdistension secondary to the use of high volumes or pressures and atelectrauma produced by repetitive alveolar opening and closure. The open lung strategy (OLA), which until now has been defined as a strategy that combines RM to open the alveolar collapse followed by a PEEP level to prevent re-collapse, aims to homogenize the lung decreasing the risk of lung injury and therefore the appearance of PPCs. However, the literature is inconclusive in the benefits that this strategy has over PPCs. There are several reasons

that could justify this lack of consensus on the results, such as the different ventilatory management of the control groups favoring more or less harmful ventilation, or the different definitions of the outcome variables used. Another cause that could also justify these results is the effectiveness of the OLA in its goal of re-expanding the lung and preventing re-collapse. In these studies, different RM have been applied as well as different PEEP adjustments, not monitoring in any of them if the patient, prior to the RM, already had an open lung condition and therefore its application was not necessary. As well as if an open lung condition was achieved with the applied maneuver or if it was maintained during surgery with the PEEP level adjusted. Moreover, most of these studies have not ensured an open lung condition after extubation and during the first hours during the postoperative period.

Therefore, we consider it necessary to conduct a study that compares an individualized and monitored perioperative open lung ventilation strategy versus a conventional standardized lung protective ventilation in patients undergoing emergency abdominal surgery with clinical signs of lung collapse.

5 References

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6. Study Hypothesis

6.1 Conceptual hypothesis

The conceptual hypothesis of the study is that, with respect to a lung condition with the presence of alveolar collapse, an individualized ventilatory strategy that maintains an open lung condition during the immediate intraoperative and postoperative period, through continuous monitoring and a perioperative individualized ventilatory approach including individualized application of recruitment maneuvers and PEEP, as well as postoperative ventilatory support in case of alveolar re-collapse, will decrease pulmonary postoperative complications and the length of stay in the ICU and in the Hospital.

6.2 Operative Hypothesis

The operative hypothesis has been formulated as a null hypothesis of no differences in postoperative complications.

7. Study Outcomes

7.1Primary Outcome:

To evaluate the efficacy of the perioperative open lung ventilatory approach, which includes intraoperative RM, individualized PEEP and individualized postoperative respiratory support, to reduce postoperative pulmonary complications during the first 7 postoperative days, compared to a conventional standardized lung protective ventilation in emergency abdominal surgery patients in whom the presence of alveolar collapse has been diagnosed through the air-test maneuver.

7.2 Secondary Outcomes:

1. To assess the benefits of a perioperative open lung condition, defined as a PaO_2/FIO_2> 400 at the end of surgery and 6h postoperatively, in the reduction of postoperative pulmonary complications during the first 7 postoperative days, compared to a non-open lung condition.
2. To assess the effectiveness of the perioperative open lung strategy, which includes intraoperative RM, individualized PEEP and individualized postoperative respiratory support, compared with the conventional standardized lung protective ventilation, to reduce postoperative pulmonary and systemic complications, ICU admissions, hospital length of stay and mortality during the first 30 postoperative days.
3. To assess the benefits of a perioperative open lung condition, defined as a PaO_2/FIO_2> 400, at the end of the surgery and 6h postoperatively, compared with a non-open lung condition in the reduction of postoperative pulmonary and systemic complications, ICU admissions, hospital length of stay and mortality during the first 30 postoperative days.

8. Ethical and Design considerations

The study has been designed in accordance with the fundamental principles set out in the Declaration of Helsinki, the European Council Convention on human rights and biomedicine, and the UNESCO Universal Declaration on the human genome and human rights, and with the requirements established by the Spanish legislation in the field of biomedical research, personal data protection and bioethics. Written informed consent will be obtained from all subjects before entering the trial. The study will be registered before patient enrolment at REec and ClinicalTrials.gov, and the protocol will be pre-published. The final protocol will be classified by the Spanish Medicines Agency and authorized by the of Ethical Research Committee of the reference center. Study reporting. This report will follow the Standard Protocol Items: CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials.
Prospective multicenter clinical trial, controlled, not masked, with random assignment of patients to two parallel ventilatory management groups (Figure 1, appendix 4).

9. Study population

Patients who meet all of the following inclusion criteria and none of the exclusion criteria will be included consecutively:

9.1 Inclusion criteria: The study population consists of adult men and women ≥18 years of age who underwent emergency abdominal surgery and sign the informed consent, with the presence of post-induction positive air-test (SpO_2 <97% after a maximum of 15 minutes at FIO_2 of 0.21) as sign of atelectasis. A SpO_2 <97% at any FIO_2 would also be considered a positive air-test.
*In those patients with pre-induction positive Air-Test, the presence of atelectasis should be confirmed with imaging techniques (CT, x-ray, LUS).
9.2 Exclusion criteria: 1) Pregnancy or breast feeding, 2) Moderate or severe ARDS defined, 3) refractory shock, 4) diagnosis or suspected intracranial hypertension (>15mmHg), 5) mechanical ventilation in the last 15 days (including CPAP), 6) presence of pneumothorax or giant bullae in a chest radiograph or computed tomography (CT).
9.3 Study discontinuation and patient withdrawal: No formal criteria will be set for stopping the study. Nevertheless, 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 Spanish law, data already collected prior and up to the date of consent withdrawal will be retained and analyzed. 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 randomized to obtain the full sample size. All randomized 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 %.

The study will be overseen by a steering committee and a data monitoring and safety committee (DMSC). The steering committee will be jointly responsible with the independent DMSC for safeguarding the interests of the participating patients. Recommendations for pausing or stopping the study will be made by the DMSC in case of safety reasons (group-difference is found in suspected unexpected serious adverse reactions or serious adverse events). The steering committee will be responsible to continue, hold or stop the study based on the DMSC recommendations.

10. Study endpoints

10.1 Main Study endpoints

A composite of severe postoperative pulmonary complications appearing during the first 7 postoperative days. Postoperative pulmonary complication will include any of the following: 1) Respiratory failure, 2) Pneumothorax, 3) Weaning failure, 4) Acute respiratory distress syndrome (ARDS), 5) Pulmonary infection.

10.2 Secondary study endpoints.

- Postoperative pulmonary complication defined as in the main endpoint but during the 30 days following the intervention.
- Postoperative pulmonary complications during the first 7 postoperative days and between days 7 and 30 after the intervention not included in the primary outcome variable. They include: 1) Atelectasis, 2) Pleural effusion, 3) Bronchospasm, 4) Aspiration pneumonitis, 5) Pulmonary thromboembolism, 6) Pulmonary edema.

-Number of severe and non-severe pulmonary complications per patient.

- Postoperative non-pulmonary complications during the first 7 postoperative days and between days 7 and 30 after the intervention. They include: 1) Cardiac ischemia, 2) de novo arrhythmia, 3) Heart failure, 4) Sepsis, 5) Septic shock, 5) Acute renal failure, 6) Surgical wound infection, 7) Urinary infection, 8) Delirium, 9) Multiorgan failure, 10) Paralytic ileus, 11) Anastomotic dehiscence, 12) Postoperative hemorrhage.

-Patients with intraoperative and postoperative rescue maneuvers.

-Composite of infectious complications

-Composite of cardiac complications

-Patients with any pulmonary and non-pulmonary complications.

-Hospital length of stay between groups and between patients with and without PPCs.

- Hospital length of stay
- Mortality within 30 days of the intervention.

10.3 Other variables and definitions.

- Age, sex, height, body weight, body mass index, ASA status, Charlson, SOFA, ARISCAT scales, Clinical Frailty scale, preoperative oxygenation (SpO_2), type of intervention, co-morbidities (pathology, medication, etc).
- Intraoperative parameters of gas exchange, acid-base state and respiratory and hemodynamic variables quantitative neuromuscular management, pharmacological reversal neuromuscular blockade, postoperative residual curarization.
- Anesthetic drugs, anesthetic techniques (epidural, paravertebral), fluid therapy and informational parameters such as surgical time, mechanical ventilation time, intraoperative bleeding, urinary output, etc.

10.4 Figure 2. Experimental schedule

	Intraoperative (Day 0)	PACU/ICU (Day 0)	Day 1	Day 3	Day 7	Day 30
PROCEDURES						
Informed consent	X					
Randomization	X					
Medical records	X	X	X	X	X	X
Baseline variables	X					
INTERVENTION						
Treatment	X	X				
SAFETY MEASURES						
Outcomes		X	X	X	X	X
ICU/HOSPITAL length of stay		X	X	X	X	X
Mortality	X	X	X	X	X	X
PRUEBAS						
Blood gas analysis	X	X				
Others (if proceeds)		X	X	X	X	X
Imaging techniques (X-ray, LUS, CT)			X	X	X	X

11. Study methodology

11.1 General management for all patients (both study groups):

*In those patients with pre-induction positive Air-Test. (SpO_2<97% with 0.21 FiO_2), the presence of atelectasis should be confirmed with imaging techniques (CT, x-ray, LUS).

• Before anesthetic induction, all patients will be pre-oxygenated with sealed mask with FIO_2 of 1.0 for 5 min.

• After orotracheal intubation, all patients in the study will be ventilated in volume-controlled mode with intraoperative VT of 8 ml/kg of ideal body weight and PEEP of 5 cmH_20 maintaining a driving pressure (DP) ≤ 12 cmH_2O. In case of DP> 12 cmH_2O, the VT will be lowered by 1 ml/Kg steps to DP ≤ 12 cmH_2O. The RR will be adjusted to guarantee normocapnia ($EtCO_2$ between 35-45 mmHg), square flow, plateau time of 10% of the inspiratory time with an inspiration: expiration (I:E) ratio of 1:2. FIO_2 of 0.21 during the first 15 minutes or up to SpO_2 <97%. Thereafter, a 0.4 FIO_2 will be adjusted.

Once the air-test has been performed, ONLY those patients with a positive post-induction air-test (SpO2 <97% at FIO2 of 0.21) as a sign of atelectasis, which is the condition for patient's recruitment and randomization, will be included in the study. At this time we will proceed to randomization.

Those patients with negative post-induction Air-Test will not be randomized. Perioperative management will be according to usual care. Data will be reported and analyzed as an exploratory analysis.

• During anesthetic emergence (when the patient begins with spontaneous ventilation) the FIO_2 will be 0.8 in all patients. The PEEP level adjusted according to protocol will be maintained until extubation.

• If necessary (due to accumulation of secretions) the aspiration will be carried out at least 10 min before extubation. After aspiration, the patient will be reconnected to mechanical ventilation and a new RM will be performed adjusting the previously programmed PEEP level.

• Once extubated, and until the arrival to the PACU, the patient will be oxygenated through a Venturi mask with FIO_2 of 0.4-0.6 up to 15-30 min after admission where the therapy will be scheduled based on randomized group.

All patients in the study will remain a minimum of 6 hours in the PACU/ICU. During the first 15-30 min the study patients will be oxygenated with a venturi mask at 15 bpm and FIO_2 0.4-0.6.

At 15-30 min the air test will be performed

- Positive Air-Test will be defined if SpO2 ≤ 96%.
- Negative Air-Test will be defined if SpO2 ≥ 97%

The Air-Test will not be performed and will be considered positive in those patients with a SpO_2 ≤ 96%.

To perform the Air-Test, the patient must meet a series of requirements:

1. Collaborative capacity with CGS> 13.
2. Richmond test score between -1 and +1.
3. VAS pain <4.

In the case that the patient requires rescue measures, these will be indicated at the discretion of the attending physician according to the protocols established in each of the participating centers.

11.2 Specific management: iOLA arm:

Intraoperative

VT of 8 ml/kg of predicted body weight and FIO_2 of 0.4. A RM will be performed and an individualized PEEP level will be adjusted (see below for detailed method) before the surgical intervention begins.

Recruitment maneuver and PEEP setting.

• Prior to performing the RM, ensure: 1) adequate hemodynamic stability (mean arterial pressure (MAP)> 70 mmHg and/or cardiac index (CI)> 2.5 ml/min/m^2) for at least 5 min prior to the maneuver and; 2) Adequate neuromuscular relaxation with 0 responses of 4, using the train of four (TOF).

• If during the RM appears hemodynamic instability (IC or MAP decrease> 50%, the maneuver will be aborted, 5-15 mg of Ephedrine or 0.05-0.15 mg of Phenylephrine will be administered and the RM will be performed again as soon as possible, so as not to lose the vasopressor effect of the drug. If hemodynamic instability appears again, the study patient will not be withdrawn (study by intention-to-treat). At 60 min, the need to perform the RM will be reassessed with an Air Test decreasing the FIO_2 (see below), without evaluating the Cdyn.

Alveolar recruitment maneuver A:

To start the RM we will change the ventilatory mode to pressure controlled ventilation (PCV) with a control pressure of 20 cmH_2O. A RR of 15 rpm, inspiration to expiration ratio of 1:1, FIO_2 of 0.8 and PEEP of 10 cmH_2O. The PEEP level will be increased from 5 in 5 cmH_2O every 3 respiratory cycles, maintaining 5 cycles in the last PEEP level (20 cmH_2O), achieving an airway opening pressure of 40 cmH_2O.

Decremental PEEP trial A:

We will change again the ventilatory mode to volume controlled ventilation (VCV) with a VT of 8 ml/Kg, RR of 15 rpm, I:E ratio of 1:1, and a PEEP of 16 cmH_2O. We will decrease the PEEP level from 2 in 2 cmH_2O every 15 seconds until we get the PEEP with better Cdyn. Once the optimum PEEP level (PEEP with better Cdyn) is known, we will perform a new RM and will adjust the PEEP level of better Cdyn.

Accidental depressurization of the airway: A new RM A will be performed achieving again an airway opening pressure of 40 cmH_2O and then adjust PEEP directly to its optimum value (better Cdyn) (See appendix 6).

Monitoring of the lung condition every 60 minutes after intubation.

• FIO_2 at 0.21 (air-test) for 5 min or up to SpO_2 <97%. If the SpO_2 falls, a new RM (RM B) will be performed, but with an airway opening pressure of 45 cmH_2O and the PEEP trial starting from PEEP of 20 cmH_20 as described below.

Alveolar Recruitment Maneuver B:

• To start the RM we will change the ventilatory mode to pressure-controlled ventilation (PCV) with a control pressure of 20 cmH_2O and PEEP of 10 cmH_2O. The PEEP level will be increased from 5 in 5 cmH_2O every 3 respiratory cycles, maintaining 5 cycles at PEEP level of 25 cmH_2O, achieving an airway opening pressure of 45 cmH_2O.

Decremental PEEP trial B:

• We will change the ventilatory mode to volume controlled ventilation (VCV) again with a VT of 8 ml/Kg and a PEEP of 20 cmH_2O. We will decrease the PEEP level from 2 in 2 cmH2O every 15 seconds until we get the PEEP with better Cdyn. Once the optimum PEEP level (PEEP with better Cdyn) is known, we will perform the described RM again and will set the PEEP level of better Cdyn.

Intraoperative rescue maneuvers:

They will be performed in case of arterial hypoxemia defined as $SpO_2 \leq 92\%$, after checking the non-existence of endobronchial IOT or bronchospasm or pneumothorax.
It will consist in the performance of the RM B and PEEP setting B. If $SpO_2 \leq 92\%$ persists, increases of FIO_2 in levels from 0.1 to FIO_2 of 1.0 are allowed.

Postoperative management:

Postoperative management A. If negative air-test (SpO_2 ≥97%) the patient will be managed with a Venturi mask with an FIO_2 of 0.4.
Postoperative management B. If positive air test (SpO_2 <97%) a high flow oxygen therapy (HFNC) will be indicated during the first 6 hours of the postoperative period with a flow rate ≥ 50 bpm and with an FIO_2 of 0.4
In the case that the patient arrives under mechanical ventilation to the PACU/ICU, the described postoperative management will begin after extubation.

11.3 Specific management STD arm:

After induction all patients will receive protection ventilation with a VT of 8 ml/kg of ideal body weight, PEEP of 5 cmH_2O and FIO_2 at 0.21 (air-test) during the first 15 min or until SpO_2 <97% Thereafter, a FIO_2 of 0.4 will be adjusted.

Monitoring of the lung condition every 60 minutes after intubation

FIO_2 at 0.21 (air-test) for 5 min or up to SpO_2 <97%.

Intraoperative rescue maneuvers:

They will be performed in case of arterial hypoxemia defined as SpO_2 ≤ 92%, after checking the non-existence of endobronchial IOT or bronchospasm or pneumothorax.
It will consist in 0.1 FIO_2 increases from 0.4 to 1.0. If hypoxemia persists PEEP will be increased 2 cmH_2O steps to a maximum of 10 cmH_2O.

Postoperative Ventilatory Management

The ventilatory management during the first 6 hours of the postoperative period will be with a Venturi mask with an FIO_2 of 0.4.
In the case that the patient arrives under mechanical ventilation to the PACU/ICU, the described postoperative management will begin after extubation.

11.4 General (all randomized patients) Postoperative rescue maneuver

In patients with persistent hypoxemia (SpO2 ≤92%) and/or hypercapnia [blood partial pressure of carbon dioxide ($PaCO_2$) >50 mmHg with a pH <7.30], tachypnea (RR >25 rpm), or increased activity of accessory respiratory muscles are present, inspiratory support with noninvasive ventilation (NIV) will be started.

Noninvasive ventilation (NIV)

The ventilator (specific for NIV or with software for NIV) and interface for NIV will be chosen by the attending physician and based on hospital availability. Positive pressure will start with an inspiratory positive airway pressure (IPAP) of 5 cmH_2O higher than the EPAP and will be increased in steps of 5 cmH_2O up to 15 cmH_2O. The EPAP will be increased to a maximum of 10 cmH_2O (15 cmH_2O if the BMI exceeds 30), FiO2 will be fixed at the discretion of the attending physician depending on the clinical response of the patient and trying to reach SpO_2 ≥97%.

Invasive ventilation

Direct tracheal intubation (without NIV trial) will be indicated if the patients also meet at least one of the following criteria:

1. Hemodynamic instability [a systolic blood pressure (SBP) <80 mmHg or <40% of the basal or vasoactive drug requirements for more than 2 h is required to maintain the SBP above 80 mmHg].
2. Ventricular arrhythmias with hemodynamic instability or ECG signs of myocardial ischemia.
3. GCS of less than 9.
4. Sedation requirement due to agitation (RASS > 3).

Tracheal intubation after 1 h of NIV will be indicated in patients meeting at least one of the following criteria:

1. Severe hypoxemia (SpO_2 <92%).
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.

12. Description of the interventions and operation of the study.

Interventions:

All patients, regardless of the study group to which they are randomized, will be provided by an extended standard of care monitoring treatments and general care.

Monitoring:

Intraoperative: ECG, pulse oximetry, capnography, bladder or esophageal temperature, invasive blood pressure, anesthetic depth through the bispectral analysis (BIS) and neuromuscular monitoring with the train of four (TOF).

During intraoperative ventilation, VT, PEEP, FIO_2, peak airway pressure (Paw), plateau pressure (Pplat), driving pressure (DP), dynamic compliance of the respiratory system (Cdyn) and respiratory System Resistance (Raw) will be monitorized and registered. The anesthetic management not related to the ventilatory management, both during the intraoperative and in the immediate postoperative period (6h), will be at the choice of the responsible physician following the protocols established in each hospital, although a series of recommendations will be established to guarantee the best treatment to all patients in the study.

13. Duration of the participation of the subjects.

Each patient will be followed for 30 days from the time of the start of anesthesia. The period between recruitment and surgical intervention may vary depending on the dynamics of each hospital.

Moments of data collection.

1. Intraoperative:
- T1. 10 min after the intubation.
- T2. At 60 minutes of mechanical ventilation.
- T3. At the end of the surgery prior to the extubation of the patient.

2. Postoperative:
- T1: At 6 h after entering URPA.
- T2: At 24 hours after the end of the surgery.
- T3: At 72 h from the end of the surgery.
- T4: At 5 days after surgery.

- T5: At 7 days after surgery.
- T6: At 30 days after surgery.

Case report form in appendix 9

14. Statistical analysis and sample size.

14.1 Sample size

The calculation of the sample size for the main objective was done assuming a 95% confidence level, a percentage of pulmonary complications of 35% at 7 days post-intervention based on the literature, and to be able to detect as significant, with a power of 80%, an absolute reduction of 10% in the incidence of pulmonary complications. Assuming 5% of possible losses, the final sample size is 732 patients (366 per group). The sample size calculation will be readjusted during the pre-planned interim analysis with the data obtained in a preliminary study (PEAL project) and the results obtained in the intermediate analysis of the study (iPROVE-EAL).

14.2 Statistical analysis of the data.

The characteristics of the patients will be described by frequencies and percentages, in the case of categorical variables, and using mean and standard deviation or median and interquartile range in continuous variables, depending on normality. Categorical variables will be compared using Chi-square test or Fisher test, and the magnitude of the association with relative risks or odds ratios will be established. Continuous variables will be compared using the Student t-test or the Mann-Whitney U test, depending on normality. The baseline characteristics of the control group and the intervention group will be compared, and in the case of finding any difference in potentially confounding variables, they will be included as adjustment variables in the corresponding multivariate models. The main outcome variable will be expressed as a proportion of complications along with a 95% confidence interval. A test of difference of proportions will be made to compare intervention group and control group. Time-to-event variables, such as time to primary or secondary outcome, will be analyzed using Kaplan-Meier curves and Cox models of proportional hazards. Variables with different measurements over time will be analyzed using mixed linear models. A significance level of $\alpha = 0.05$ will be considered.

14.3 Methods for missing data

Missing primary outcome data:

We do not expect missing data on the primary outcome measure and only complete case-analysis will be performed.

Missing secondary outcomes data:

Only complete case analysis will be made.

All analyzes will be done by intention to process and the missing data will be imputed using multiple imputation methods when more than 5% appear in the primary or secondary outcome variables.

15. Method of randomization and minimization of biases.

15.1 Randomization:

Those patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized (after obtaining informed consent) to one of the two treatment groups: iOLA and STD.

The randomization will be done online through www.iprove-network.es following the Mersenne Twister algorithm. In addition, through the website the investigators will download the study documents, consultation of training videos, consultation of IPs to the coordinating center, etc.

15.2 Masking:

The characteristics of the study do not allow the masking of the researchers during the intraoperative and immediate postoperative period. A second investigator, masked for the randomization arm will be the responsible for the recording of the primary and secondary outcomes. Moreover, both groups will be masked for the researchers who perform the statistical analysis and the promoter of the study (except for the analyzes at the pre-specified times).

16. Severe Adverse Events (SAEs)

A special sheet has been designed to document adverse events. An adverse event is defined as any medical episode that occurs, whether or not related to conventional or individualized mechanical ventilation, and that is not related to the patient's clinical status. Based on current knowledge, it is not estimated that patients present adverse events in relation to this study that are different from those that may be presented by any mechanically ventilated patient during Lung Recruitment Maneuvers who does not participate in this study. The possible adverse events related to RMs that may appear are hemodynamic instability and exceptionally electrical cardiac alteration that associates hemodynamic instability, and pneumothorax. In case these appear, as during standard clinical management, immediate treatment will be given. Severe adverse events shall be documented in the specific CRF.

17. Monitoring plan

The monitoring plan is based on the modification of the Haybittle-Peto limits for trial cessation after the intermediate analysis in the second half of the inclusion period. The analysis of the main outcome variable will be presented to the Data and Safety Management Committee (DSMC) blindly to the study groups. The intermediate analysis will be performed once the efficacy variables of the first 366 patients are obtained. If the intermediate analysis is significant (P <0.001) both positively and negatively for the intervention group, the DSMC may stop the inclusion of new patients.
The trial will be externally monitored according to the GCP Directive and the monitoring and data verification plan. After the consent is obtained, we will use central monitoring of site through the eCRF, including adherence to the protocol.

18. Quality control and quality assurance

The principal investigator and his team will be responsible for organizing the trial sites including education of the local investigators, the trial site staff and clinical staff before the initiation of the trial.
After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of participants and entry of data. Clinical staff at the trial sites will be responsible for screening of eligible patients and the treatment of trial participants.

19. Limitations and Strengths of the Study

19.1 Potential limitations: No clinical limitations have been identified for this study in any of its two phases. The only potential limitation could be due to the hemodynamic inestability of the patient during the intraoperative period not allowing the RM and PEEP trial, or the patient's refusal to non-invasive ventilation during the postoperative period.

19.2. Strength and impact: As far as we know this is the first study planned in two phases. A first phase that will describe the incidence of complications in the study population, the associated factors and the ventilatory management in patients undergoing emergency laparotomy, and a second randomized phase that will evaluate the benefits of the perioperative personalized open lung strategy at a multicenter level. If our hypothesis is correct, this strategy will have a considerable impact on the reduction of postoperative complications, reducing ICU and hospitalization length of stay and health costs. It will also be the first study that prospectively evaluates the benefits of maintaining an open lung condition, regardless of the ventilatory management of the patient.

20. Ethical aspects.

This study will respect the fundamental principles established in the Declaration of Helsinki, in the European Council Convention on human rights and biomedicine in the Unesco Universal Declaration on human genome and human rights, as well as the requirements established by Spanish legislation in the field of biomedical research, personal data protection and bioethics. It will be submitted for authorization to the Ethical Research Committee (EC). Only patients who sign informed consent will be included in the study. At all times, confidentiality and data security will be maintained. The promoter of the study will be responsible for the preservation of records in each center and for the publication policy.

21. Dissemination of research results and sub-studies

The Scientific Committee will appoint a Drafting Committee to draft the scientific report (s) of this research, which will be disseminated in a timely manner. It is expected that a series of secondary analyzes will be carried out. Researchers will have priority to direct this type of analysis and are encouraged to do so. Participation will be based on the contribution to the study in its two phases. The Steering Committee will consider the scientific validity and the possible effect on the anonymity of the participating centers before the granting of any of these applications. If necessary, a prior written agreement will establish the terms of this type of collaboration. The Scientific Committee must approve the final version of all manuscripts, before submission. In case of disagreement within the Steering Committee, the head of the investigation will make a decision. Any data from the PEAL and iPROVE-EAL analysis with the incorporation of two or more study sites will be considered for possible secondary analyzes and will be subject to predefined rules.
All participants in the study will be included as co-authors under the iPROVE Network Group.

22. Data management and data ownership

The promoter of the study, the iPROVE Group, will act as custodian of the data. In line with the principles of preservation and exchange of data, the Steering Committee, after the publication of the general database, will consider all reasonable requests to carry out the secondary analyzes (sub-studies). The main consideration for these types of decisions will be the quality and validity of any analysis that is proposed. Only summary data will be presented publicly and all data at International, national, institutional and patient level will be strictly anonymous. The data of the individual patients provided by the participating hospitals are property of the respective institution. Once each local coordinator has confirmed that the data provided from their hospital is both complete and accurate, they will be transferred to an online data database. The complete data set

of the participants with respect to the patients, the hospitals and the communities will be codified, however, they will be made freely available to the public for two years following the publication of the main scientific report. Prior to this, the Scientific Committee is under no obligation to publish the data to any collaborator or third party if they believe that this is not in line with the broader objectives of the project.

23. Legal and organizational aspects.

23.1 Trial funding

The trial is not founded yet.

23.2 Compensation

Neither the trial sites, researchers nor patients will receive compensations.

23.3 Insurance

For all those centres that require it, civil liability insurance will be provide by the study sponsor.

ANA LUCIA ARELLANO ANDRINO, Secretario del **Comité de Ética de la Investigación con medicamentos del Hospital Clínic de Barcelona**

Certifica:

Que este Comité ha evaluado la propuesta del promotor, para que se realice el estudio:

CÓDIGO:
DOCUMENTOS CON VERSIONES:

Tipo	Subtipo	Versión
Protocolo		Version 03.0 data: 12-february-2020
Hoja Información de Paciente		Versión 04.0 – abril 2020

TÍTULO: Postoperative pulmonary complications in emergency abdominal surgery. Incidence, risk factors and personalized protective ventilatory strategies.
PROMOTOR:
INVESTIGADOR PRINCIPAL: CARLOS FERRANDO ORTOLÁ

y considera que, teniendo en cuenta la respuesta a las aclaraciones solicitadas (si las hubiera), y que:

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Que se han evaluado la compensaciones económicas previstas (cuando las haya) y su posible interferencia con el respeto a los postulados éticos y se consideran adecuadas. - Que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este centro.
- Que dicho estudio cumple con las obligaciones establecidas por la normativa de investigación y confidencialidad que le son aplicables.
- Que dicho estudio se incluye en una de las líneas de investigación biomédica acreditadas en este centro, cumpliendo los requisitos necesarios, y que es viable en todos sus términos.

Este CEIm acepta que dicho estudio sea realizado, debiendo ser comunicado a dicho Comité Ético todo cambio en el protocolo o acontecimiento adverso grave.

y hace constar que:

Reg. HCB/2020/0030

HOSPITAL CLÍNIC DE BARCELONA
Villarroel, 170 – 08036 Barcelona (España)
Tel. 93 227 54 00 Fax 93 227 54 54

1º En la reunión celebrada el día 30/01/2020, acta 2/2020 se decidió emitir el informe correspondiente al estudio de referencia.
2º El CEIm del Hospital Clínic i Provincial, tanto en su composición como en sus PNTs, cumple con las normas de BPC (CPMP/ICH/135/95) 3º Listado de miembros:

Presidente:
- JOAQUIM FORÉS I VIÑETA (Médico Traumatólogo, HCB)

Vicepresidente:
- ANDREA SCALISE (Médico Farmacólogo Clínico, HCB)

Secretario:
- ANA LUCIA ARELLANO ANDRINO (Médico Farmacólogo Clínico, HCB)

Vocales:
- ITZIAR DE LECUONA (Jurista, Observatorio de Bioética y Derecho, UB)
- MONTSERRAT GONZALEZ CREUS (Trabajadora Social, Servicio de Atención al Usuario, HCB)
- JOSE RIOS GUILLERMO (Estadístico. Plataforma de Estadística Médica. IDIBAPS)
- OCTAVI SANCHEZ LOPEZ (Representante de los pacientes)
- MARIA JESÚS BERTRAN LUENGO (Médico Epidemiólogo, HCB)
- JOAQUÍN SÁEZ PEÑATARO (Médico Farmacólogo Clínico, HCB)
- SERGI AMARO DELGADO (Médico Neurólogo, HCB)
- JULIO DELGADO GONZÁLEZ (Médico Hematólogo, HCB)
- EDUARD GUASCH CASANY (Médico Cardiólogo, HCB)
- VIRGINIA HERNANDEZ GEA (Médico Hepatólogo, HCB)
- MARINA ROVIRA ILLAMOLA (Farmacéutico Atención Primaria, CAP Eixample)
- MIRIAM MENDEZ GARCÍA (Abogada, HCB)
- JOSE TOMAS ORTIZ PEREZ (Médico Cardiólogo, HCB)
- BEGOÑA GOMEZ PEREZ (Farmacéutica Hospitalaria, HCB)
- ELENA CALVO CIDONCHA (Farmacéutica Hospitalaria, HCB)
- CECILIA CUZCO CABELLOS (Enfermera, HCB)

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, este se ausentará de la reunión durante la discusión del proyecto.

Para que conste donde proceda, y a petición del promotor,

ANA LUCIA ARELLANO ANDRINO
por ANA LUCIA ARELLANO ANDRINO
Fecha: 2020.05.21 14:37:20 +02'00'
Firmado digitalmente

Reg. HCB/2020/0030

Barcelona, a 20 de mayo de 2020

HOSPITAL CLÍNIC DE BARCELONA
Villarroel, 170 - 08036 Barcelona (España)
Tel. 93 227 54 00 Fax 93 227 54 54

APPENDIX 2: AEMPS study classification

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO
DE MEDICAMENTOS
DE USO HUMANO

DESTINATARIO:

D. CARLOS FERRANDO ORTOLÁ
Sº ANESTESIOLOGÍA Y REANIMACIÓN
HOSPITAL CLINIC
VILLARROEL, 170
08036 - BARCELONA

Fecha: 2 de septiembre de 2019

REFERENCIA:ESTUDIO iPROVE-ELA

ASUNTO: NOTIFICACIÓN DE PROPUESTA DE RESOLUCION DE CLASIFICACIÓN DE ESTUDIO CLÍNICO O EPIDEMIOLÓGICO

Adjunto se remite propuesta de resolución de clasificación sobre el estudio titulado **"COMPLICACIONES PULMONARES POSOPERATORIAS EN CIRUGÍA ABDOMINAL URGENTE. INCIDENCIA, FACTORES ASOCIADOS Y ESTRATEGIAS VENTILATORIAS DE PREVENCIÓN".**

CORREO ELECTRÓNICO
farmacoepi@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

iPROVE-EAL

Individualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial

Investigator Information Brochure PEAL + iPROVE-EAL

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

A) Definition of complications

Pulmonary Complications

	PEAL + iPROVE-EAL
Atelectasis	Combination of $SpO_2 \leq 96\%$ during the air test and chest radiography with lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung
Hypoxemia or Mild respiratory failure	$SpO_2 < 92\%$ or $PaO_2 < 300$mmHg with FiO_2 of 0.21
Severe respiratory failure	Increased FiO_2, increased requirement for CPAP, or the need for noninvasive or invasive ventilation
Weaning failure	Reintubation within the first 48h after postoperative extubation.
ARDS	● **Mild**: $PaO_2/FiO_2 < 300$ mmHg with CPAP ≥ 5 cmH_2O y $FiO_2 \geq 0.5$. ● **Moderate:** $PaO_2/FiO_2 < 200$ mmHg with PEEP ≥ 5 cmH_2O y $FiO_2 \geq 0.5$. ● **Severe**: $PaO_2/FiO_2 < 100$ mmHg with PEEP ≥ 5 cmH_2O y $FiO_2 \geq 0.5$. Acute (within one week) symptoms with bilateral pulmonary opacities
Pulmonary infection	Presence of a new pulmonary infiltrate and/or progression of previous pulmonary infiltrates on a chest radiograph plus at least two of the following criteria: (a) leukocytosis with > 12,000 WBC/mm^3 or leukopenia with < 4000 WBC/mm^3, (b) fever > 38.5°C or hypothermia < 36°C, and (c) increased secretions with purulent sputum and a positive bronchial aspirate
Pleural effusion	Chest radiography with the presence of costophrenic angle blunting, displacement of adjacent anatomical structures, and blunting of the hemidiaphragmatic silhouette in the supine position
Pneumothorax	Chest radiography with air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Presence of expiratory wheezing treated with bronchodilator
Aspiration pneumonitis	Respiratory failure after the inhalation of regurgitated gastric contents
Pulmonary edema	Fluid accumulation in the alveoli due to poor cardiac function diagnosed with chest radiography of lung ultrasound.
Pulmonary embolism	A new blood clot or thrombus within the pulmonary arterial system.

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

Systemic Complications

	PEAL + iPROVE-EAL
Severe sepsis	Infectious focus identified plus organ dysfunction (defined as an increase in SOFA ≥2).
Septic shock	Severe sepsis with hypotension and hypoperfusion that is unresponsive to fluids.
Surgical site infection	The CDC defines a superficial incisional surgical site infection as one which meets the following criteria. (1) Infection occurs within 30 days after surgery and (2) Involves only skin and subcutaneous tissue of the incision and (3) The patient has at least one of the following: (a) purulent drainage from the superficial incision (b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision (c) at least one of the following symptoms or signs of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture negative finding does not meet this criterion. (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.
Urinary tract infection	A simplified version of the CDC recommendations defines a urinary tract infection as follows: a positive urine culture of 105 colony forming units ml1 with no more than two species of microorganisms, and with at least one of the following symptoms or signs: fever (> 38.8ºC), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause.
Arrhythmia	ECG evidence of cardiac rhythm disturbance.
Myocardial infarction	Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:10 symptoms of ischaemia; new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus at angiography or autopsy
Heart failure	Cardiac index <2.5 ml/min/m^2 or >2.5 when ≥5 µg/kg/min dobutamine is required. Clinical signs (hypotension, oliguria, pulmonary edema) together with NT-proBNP >13 pg/ml or echocardiographic diagnosis.
Acute kidney injury	AKIN scale: ● **Stage I**: Diuresis < 0,5 mg/Kg (6h) or increase in serum Cr > 0,3 mg/dl.

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

- **Stage II**: Diuresis < 0,5 mg/Kg (12h) or basal Cr x 2 mg/dL.
- **Stage III**: Diuresis < 0,3 mg/Kg (24h) o anuria (12h) or basal Cr x 3 mg/dL, or Cr > 4 mg/dL or renal replacement therapy.

Delirium	Positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (see information brochure)
Paralytic ileus	Failure to tolerate solid food or defecate for three or more days after surgery
Postoperative hemorraghe	blood loss within 72 h after the start of surgery which result in transfusion of blood or a drop in hemoglobin > 7gr/dL
Anastomotic breakdown	Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicemia, metabolic disturbance and/or multiple organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localized area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak.

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

B) Online randomization and study website

In order to facilitate various procedures for researchers, the PEAL and the iPROVE-EAL trial makes available the website from which it is possible to download patient information sheets, data collection notebooks and other documentation of interest related to the project.

The randomization of patients must be done through an online application which is accessed from the website, in the section "RANDOMIZATION AREA". To enter it, the user must enter with their own password provided. Then, clicking on the link "Access to the randomization application" the website will launch a form where the center code that was provided and the patient code should be written according to the established coding. Pressing the button will execute the randomization that will be stored in the database, and the result of the group to which the patient has been assigned will appear on the screen, with the option of printing it**. IMPORTANT: Only one randomization per patient must be done through the web application.** Launching the application more than once for the same patient code can lead to errors in the subsequent analysis of the results of the data collected in your center. To avoid errors, there is a link which can be used to perform randomization tests without sending or storing results.

- The code of your center is the same user with which the private area is accessed.

- The patient code has the structure "pac", followed by a 3-digit number that represents the number of the patient recruited in your center. For example: pac-002, pac-123 ...

On this website, you can also download paper data collection forms. However, once completed, the researcher must download the digital data collection forms, in Microsoft Word format, prepared to facilitate the entry of paper data into electronic format.

THE WEBSITE WILL BE READY IN FEW WEEKS. THEN, MORE ACCURATE INFORMATION FOR USER WILL BE GIVEN.

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

C) Scales and calculations

Body mass index (BMI): Kg/m^2

Predicted body weight (PBW):

men: PBW (kg) = 50 + 0.91 (height in cm-152)

women: PBW (kg) = 45.5 + 0.91 (height in cm-152)

8 ml/kg PBW in men				**8 ml/kg PBW in women**		
162 cm 470 ml	164 cm 485 ml	166 cm 500 ml		153 cm 370 ml	155 cm 385 ml	157 cm 400 ml
168 cm 515 ml	170 cm 530 ml	171 cm 535 ml		159 cm 415 ml	160 cm 420 ml	161 cm 425 ml
172 cm 540 ml	173 cm 550 ml	174 cm 560 ml		162 cm 435 ml	163 cm 440 ml	164 cm 450 ml
175 cm 565 ml	176 cm 570 ml	177 cm 580 ml		165 cm 455 ml	166 cm 465 ml	167 cm 470 ml
178 cm 585 ml	179 cm 595 ml	180 cm 600 ml		168 cm 475 ml	169 cm 485 ml	170 cm 490 ml
182 cm 615 ml	184 cm 630 ml	186 cm 645 ml		171 cm 500 ml	172 cm 505 ml	174 cm 520 ml
188 cm 660ml	190 cm 670 ml	192 cm 685 ml		176 cm 530 ml	178 cm 550 ml	180 cm 565 ml

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

ASA physical status classification system

ASA I	**A normal healthy patient.** Healthy, non-smoking, no or minimal alcohol use
ASA II	**A patient with mild systemic disease.** Only mild diseases without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	**A patient with severe systemic disease.** Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	**A patient with severe systemic disease that is a constant threat to his life.** Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis

Visual Analog Scale (VAS)

The VAS scale allows to measure the pain intensity that the patient describes with the maximum reproducibility among the observers. It consists of a horizontal line of 10 centimeters, at the ends of which are the extreme expressions of a symptom. On the left is the absence of pain or less intensity. The patient is asked to mark the point indicating the intensity on the line and it is measured with a millimeter ruler. The intensity is expressed in centimeters or millimeters.

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

Charlson comorbidity index

Clinical condition	Weight
- Myocardial infarct, Congestive cardiac insufficiency, peripheral vascular disease, cerebrovascular disease. - Dementia - COPD - Ulcers - Conjunctive tissue disease - Cirrhosis or chronic disease of the liver - Diabetes	**1**
- Hemiplegia - Moderate or severe kidney disease - Diabetes with organ complication - Tumor/Leukemia/Lymphoma	**2**
- Moderate or severe liver disease	**3**
- Malignant tumor, metastasis, AIDS	**6**

Apfel score for PONV

Risk factors	Points	Risk factors	Points
Female gender	1	**Postoperative Opioids**	1

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

Non-smoker	1	**Sum=**	0……..4
History PONV	1		

SOFA (Sequential Organ Failure Assessment) SCORE

System					
	0	**1**	**2**	**3**	**4**
Cardiovascular	MAP > 70 mmHg	MAP < 70 mmHg	Dopamine≤5 µg/kg/min or dobutamine (any dose)	Dopamine>5 or epinephrine≤0.1 or norepinephrine ≤0.1	Dopamine>5 or epinephrine >0.1 or norepinephrine >0.1
Respiratory (PaO_2/FiO_2)	>400	301-400	201-300	101-200	≤ 100
Hepatic (bilirrubin,µmol/l mg/dl	≤ 20 <1.2	20-32 1.1-1.9	33-101 2.0-5.9	102-204 6.0-11.9	>204 >12.0
Kidney (creatinine, µmol/l) mg/dl	≤ 110 <1.2	110-170 1.2-1.9	171-299 2.0-3.4	300-440; 3.5-4.9; or urine output ≤500 ml/d	>440; >5.0; or urine output <200 ml/d
Coagulation (platelets, x 10^{3}/microL)	>150	≤150	≤100	≤50	≤20
SNC (Glasgow Coma Scale)	15	13-14	10-12	6-9	<6

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

ARISCAT Score

Age	≤ 50	0
	51-80	3
	≥ 80	16
Preoperative SpO_2	≥ 96	0
	91- 95	8
	≤ 90	24
Respiratory infection (last month)		17
Preoperative hemoglobin (≥ 10 g/dl)		11
Surgical incision	Peripherical	0
	Abdominal	15
	Intrathoracic	24
Duration of surgery (h)	≤ 2	0
	> 2 a 3	16
	> 3	23
Emergency surgery		8

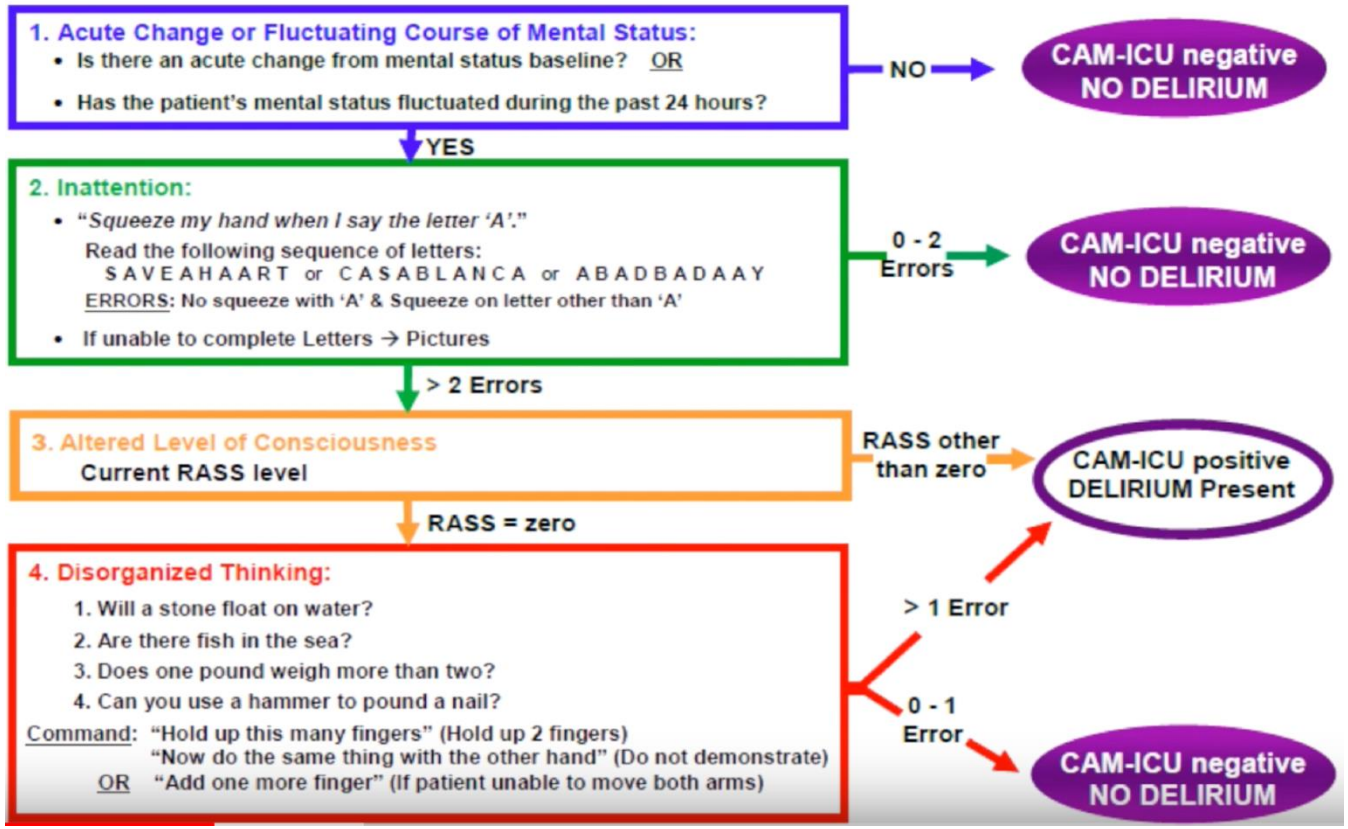
APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

Richmond Agitation Sedation Scale (RASS)

Score	Term	Description
+4	**Combative**	Overtly combative or violent; immediate danger for the staff
+3	**Very agitated**	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff
+2	**Agited**	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	**Restless**	Anxious or apprehensive movements but not aggressive or vigorous
0	**Alert and calm**	Spontaneously pays attention to caregiver
-1	**Drowsy**	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	**Light sedation**	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	**Moderate sedation**	Any movement (but no eye contact) to voice
-4	**Deep sedation**	No response to voice, but any movement to physical stimulation
-5	**Unarousable**	No response to voice or physical stimulation

APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

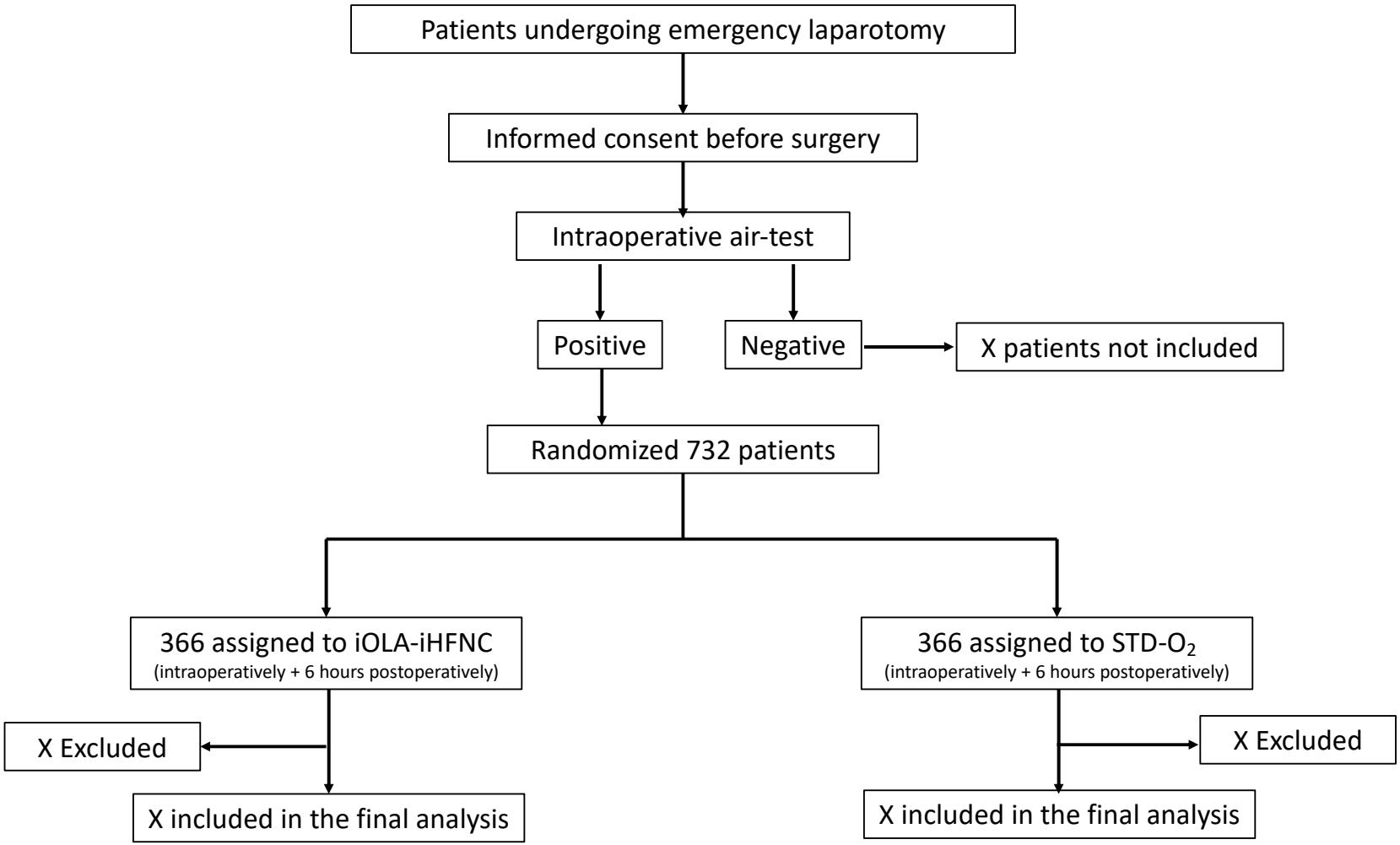
CAM-ICU scale



APPENDIX 3: INVESTIGATOR INFORMATION BROCHURE (Trial definitions)

CLINCAL FRAILTY SCALE		
Very fit	Robust, active, energetic, motivated. Exercise regularly.	**1.** ☐
Well	No active disease symptoms. Exercise or very active occasionally.	**2.** ☐
Managing well	Well controlled medical problems. Not regularly active (walking).	**3.** ☐
Vulnerable	Symptoms limit activities, but not dependent on others for daily help.	**4.** ☐
Mildly frail	Evident slowing and need help in instrumental activities of daily living (controlling medication, finances, transportation, heavy housework). Typically impairs shopping, walking outside alone, meal preparation and housework.	**5.** ☐
Moderately frail	Need help with all outside activities and housekeeping. Often have problems with stairs and need help with bathing and getting dressed.	**6.** ☐
Severely frail	Completely dependent for personal care, any physical or cognitive activity. Stable, not at high risk of dying within 6 months.	**7.** ☐
Very severely frail	Completely dependent, approaching the end of life. Typically, they could not recover from a minor illness.	**8.** ☐
Terminally ill	Approaching the end of life. Life expectancy < 6 months.	**9.** ☐

APPENDIX 4: CONSORT FLOWCHART



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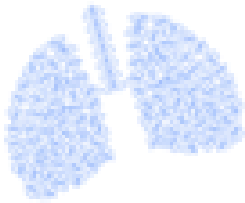
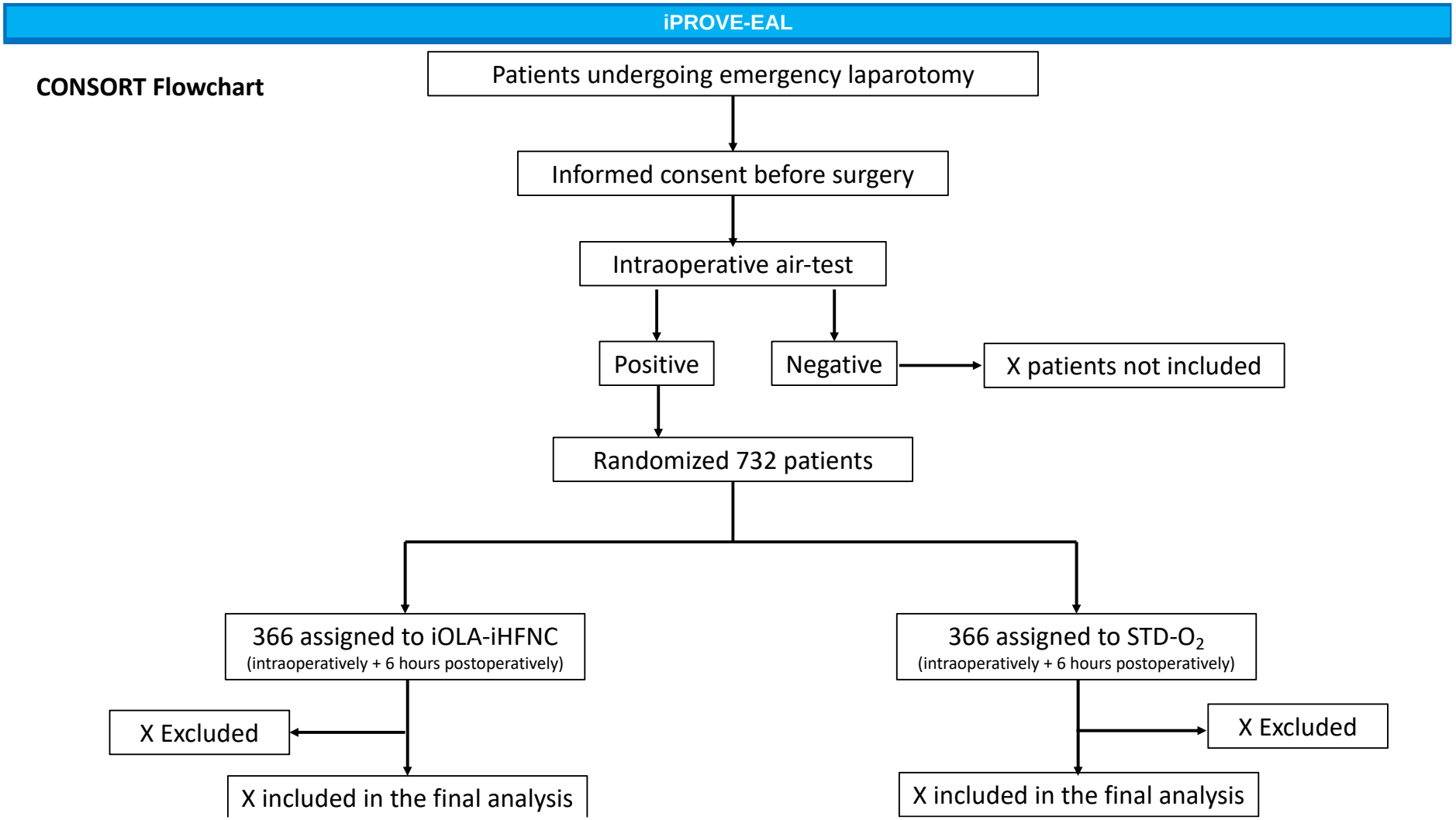
www.iprove.incliva.es



Study Protocol

iPROVE-EAL Trial

APPENDIX 5: Printable Cards



APPENDIX 5: Printable Cards

iPROVE-EAL

General Ventilatory Management

PRE-OXYGENATION: 5 minutes with 1.0 FIO_2

VENTILATORY SETTING: VT 8 ml/Kg **ideal body weight**

PEEP: 5 cmH_2O

RR to $etCO_2$ 35-45 mmHg

Plateau pause: 10% I:E= 1:2

Air-test

FIO_2 = 0.21 during the first 15 minutes or up to SpO_2 < 97%

Thereafter, the FIO_2 of 0.4 will be adjusted

Inclusion criteria

Positive air test = SpO_2 < 97% → RANDOMIZATION

Negative air-test = SpO_2 >=97% → NOT INCLUDED (Data will be reported)

APPENDIX 5: Printable Cards

INTRAOPERATIVE ventilatory management

STD-02 GROUP

General Ventilatory Management

VENTILATORY SETTING: VT = 8 ml/Kg **ideal body weight** *

FIO_2 = 0.4

PEEP: 5 cmH_2O

RR to $etCO_2$ 35-45 mmHg

Plateau pause: 10% I:E= 1:2

* If DP > 12 cmH_2O = decrease VT in 1 ml/kg steps until DP ≤ 12 cmH_2O

Monitoring of lung condition every 60 minutes

FIO_2 = 0.21 (air-test) for 5 minutes or up to SpO_2 < 97%

Rescue maneuver if SpO_2 <92%.

Rescue Maneuvers *

1. Increase FIO_2 in 0.1 steps
2. Increase PEEP in 2 steps until 10 cmH_2O

* The change from one level to another is made if the SpO_2 persists < 92%

Extubation maintaning the level of PEEP/CPAP

APPENDIX 5: Printable Cards

POSTOPERATIVE ventilatory management
STD-02 GROUP

General management

- All the patients will stay at PACU or ICU at least 6 hours
- From extubation and during the first 15-30´ all the patients will be oxygenated with 0.4-0.6 FiO_2

*15-30 min after PACU/ICU admission an **Air-Test** (breathing room-air for 5 minutes) will be performed*

Ventury mask with 0.4 FIO_2 during 6 hours.

If SpO_2 <92% postoperative rescue maneuvers will be initiated (See protocolo)

APPENDIX 5: Printable Cards

INTRAOPERATIVE ventilatory management

iOLA-iHFNT GROUP

General Ventilatory Management

VENTILATORY SETTING: VT = 8 ml/Kg **ideal body weight** *

FIO_2 = 0.4

RECRUITMENT MANEUVER A + PEEP SETTING A (see template)

RR to $etCO_2$ 35-45 mmHg

Plateau pause: 10% I:E= 1:2

* If DP > 12 cmH_2O = decrease VT in 1 ml/kg steps until DP ≤ 12 cmH_2O

Monitoring of lung condition every 60 minutes

FIO_2 = 0.21 (air-test) for 5 minutes or up to SpO_2 < 97%

Positive air-test (SpO_2 <97 while breathing 0.21 FIO_2)

RECRUITMENT MANEUVER A + PEEP SETTING A (see template)

Rescue maneuver if SpO_2 <92%.

Rescue Maneuvers *

1. **RECRUITMENT MANEUVER B + PEEP SETTING B (see template)**
2. Increase FIO_2 in 0.1 steps

* The change from one level to another is made if the SpO_2 persists < 92%

Extubation maintaning the level of PEEP/CPAP

APPENDIX 5: Printable Cards

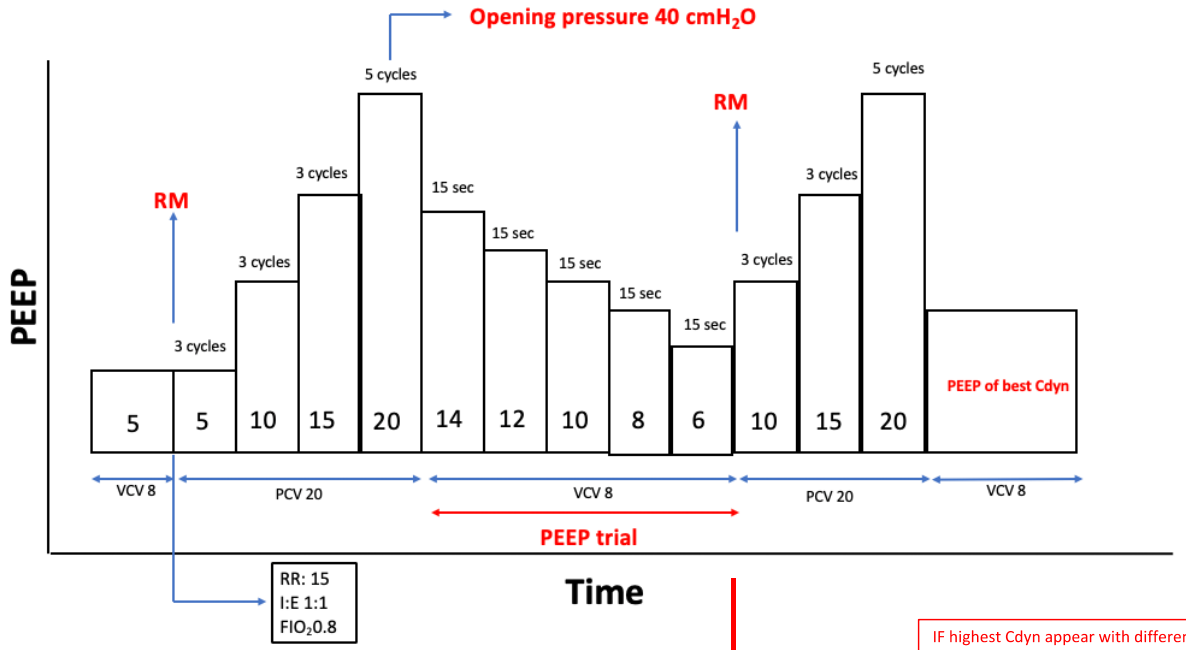
RECRUITMENT MANEUVER A + PEEP SETTING A

Clinical conditions for the RM

- MAP >70 mmHg and or CI >2,5 ml/min/m^2,
- Adequate neuromuscular block with 0 of 4 (TOF).

If CI or MAP >50% during the RM:

Stop the RM and administer 5-15 mg de Ephedrine or 0,05-0,15 mg of phenilephrine. Thereafter re-start de RM.



IF highest Cdyn appear with different PEEP values, select PEEP of lowest driving pressure (Pplat –PEEP)
IF Airway despresurization:

- New RM and same PEEP level.

APPENDIX 5: Printable Cards

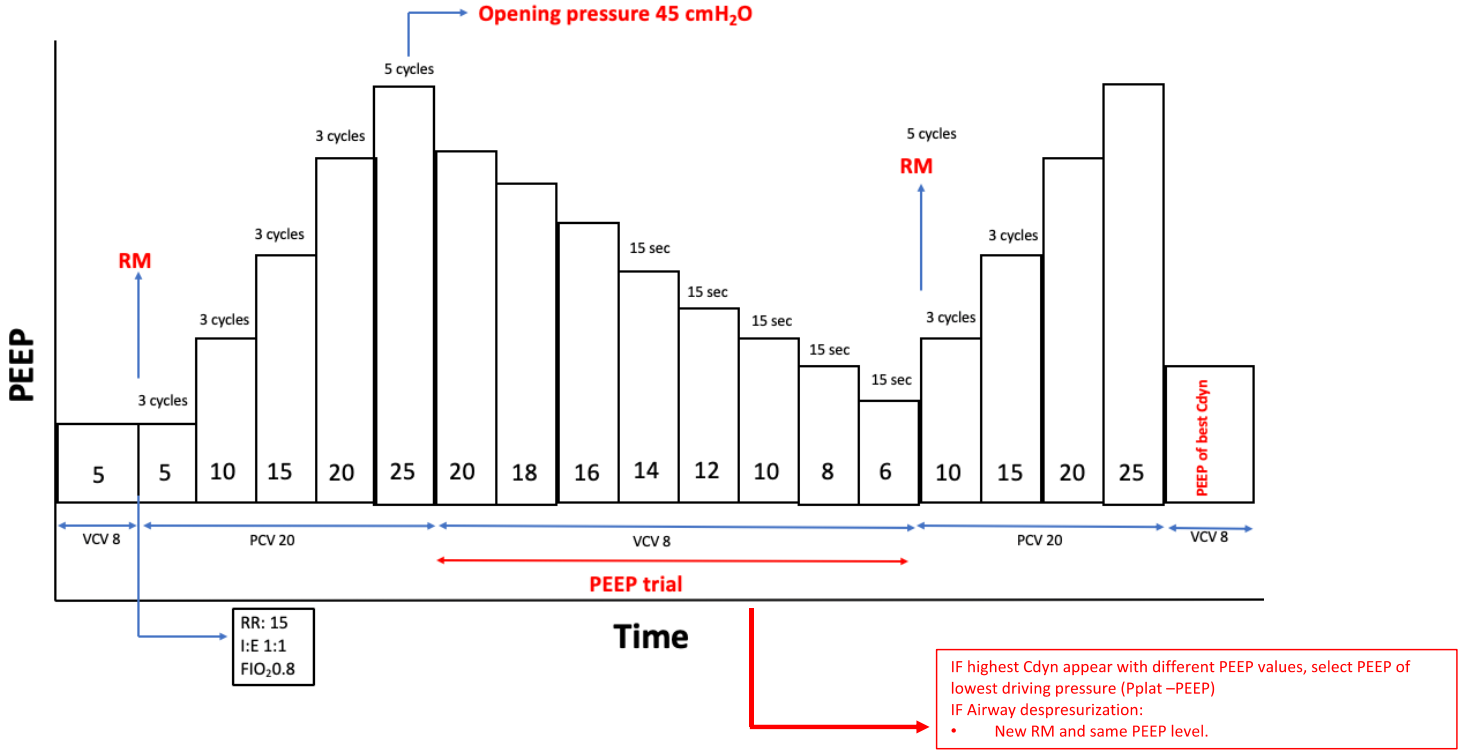
RECRUITMENT MANEUVER B + PEEP SETTING B

Clinical conditions for the RM

- MAP >70 mmHg and or CI >2,5 ml/min/m^2,
- Adequate neuromuscular block with 0 of 4 (TOF).

If CI or MAP >50% during the RM:

Stop the RM and administer 5-15 mg de Ephedrine or 0,05-0,15 mg of phenilephrine. Thereafter re-start de RM.



IF highest Cdyn appear with different PEEP values, select PEEP of lowest driving pressure (Pplat –PEEP)
IF Airway despresurization:

- New RM and same PEEP level.

APPENDIX 5: Printable Cards

POSTOPERATIVE ventilatory management

iOLA-iHFNT GROUP

General management

- All the patients will stay at PACU or ICU at least 6 hours
- From extubation and during the first 15-30´ all the patients will be oxygenated with 0.4-0.6 FiO_2

*15-30 min after PACU/ICU admission an **Air-Test** (breathing room-air for 5 minutes) will be performed **

Positive Air-test = High-flow nasal cannula with a flow rate of ≥ 50 lpm FIO_2 with 0.4 FIO_2 during 6 hours.

Negative Air-test = Ventury mask with 0.4 FIO_2 during 6 hours.

** To perform the Air-Test, the patient must meet a series of requirements:*

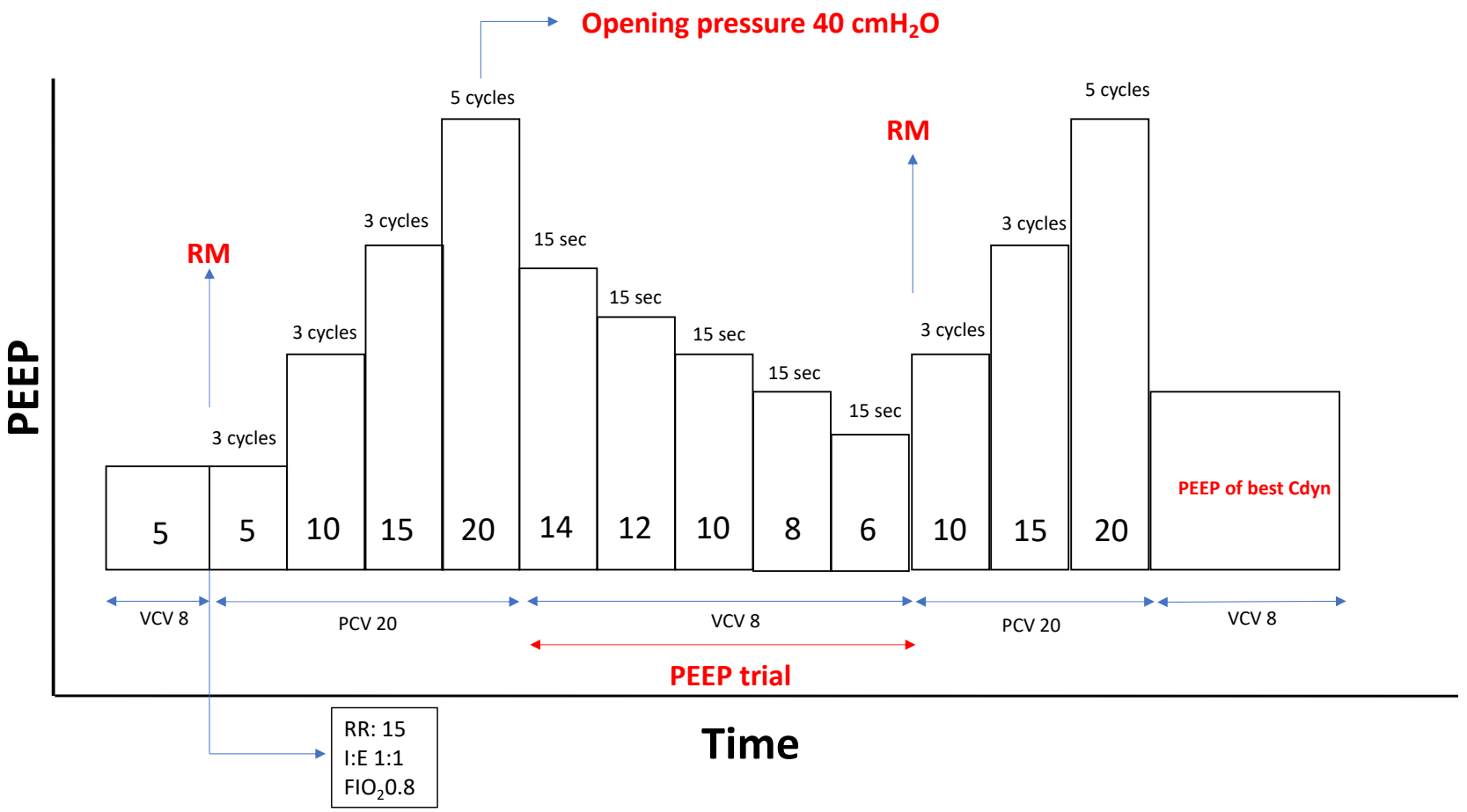
1. Collaborative capacity with CGS> 13.

2. Richmond test score between -1 and +1.

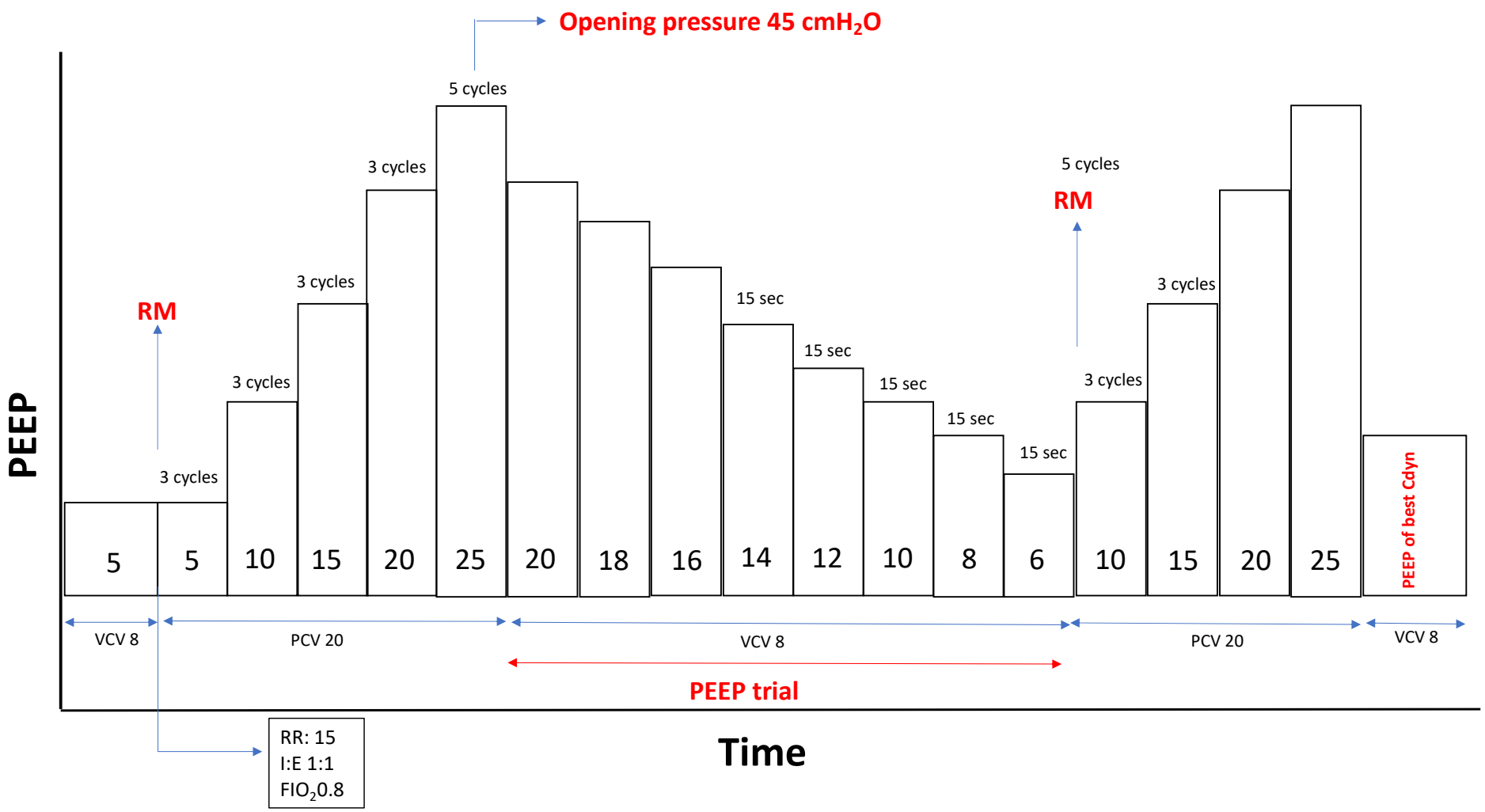
3. VAS <4.

If SpO_2 <92% postoperative rescue maneuvers will be initiated (See protocolo)

APPENDIX 6: Recruitment Maneuver (RM) A



APPENDIX 6: Recruitment Maneuver (RM) B



APPENDIX 7: Charter for the independent data monitoring and safety comitee (DMSC)

Individualized PeriopeRative Open lung VEntilatory approach in Emergency Abdominal Laparo-tomy/scopy. A prospective international randomized controlled trial.

Protocol version: IPROVE-EAL. Version 03.0 data: 11-february-2020

Sponsor: Department of Anesthesiology and Critical Care, Hospital Clinic de Barcelona.

Protocol registration numbers:

Clinicaltrials.gov identifier: NCT04229810
Ethics Committee number: HCB/2020/0030

APPENDIX 7: Charter for the independent data monitoring and safety comitee (DMSC)

Introduction

The Data Monitoring and Safety Committee (DMSC) will constitute its own plan of monitoring and meetings. However, this charter defines the minimum of obligations and primary responsibilities of the DMSC, its relationship with other trial components, its membership, and the purpose and timing of its meetings, as perceived by the iPROVE-EAL Steering Committee. The charter also outlines the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC are responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the trial. The DMSC will provide recommendations about stopping or continuing the trial to the Steering Committee of the iPROVE-EAL trial. The DMSC may also – if applicable - formulate recommendations related to the selection/recruitment/retention of participants, their management, adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the iPROVE-EAL Steering Committee. The Steering Committee will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically or by phone at their own discretion in order to evaluate the planned interim analyses of the iPROVE-EAL trial. The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail to discuss the safety for trial participants. The DMSC can, at any time during the trial, request information about the distribution of events, including outcome measures and serious adverse events (SAEs) according to group allocation. Further, the DMSC can request unmasking of the interventions, if deemed important (see section on ‘closed sessions’). The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the iPROVE-EAL Steering Committee. As fast as possible, and no later than 48 hours, the Steering Committee has the responsibility to inform all trial sites and investigators, about the recommendation of the DMSC and the Steering Committee decision hereof.

APPENDIX 7: Charter for the independent data monitoring and safety comitee (DMSC)

Members of the DMSC

The IDMSC is an independent multidisciplinary group consisting of three clinicians and a biostatistician that, collectively, has experience in the conduct, monitoring and analysis of randomized clinical trials.

DMSC Clinicians

To be nominated in due time

DMSC Biostatistician

To be nominated in due time

Conflicts of interest

The members of the DMSC will fill-in and sign a conflicts of interest form. DMSC membership is restricted to individuals free of conflict of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, or individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. Furthermore, the DMSC members do not own stocks in the companies having products being evaluated by the iPROVE-EAL trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organization (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The IDMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the trial. Any DMSC members who develop significant conflicts of interest during the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the trial, the Steering Committee will appoint the replacement(s).

Formal interim analysis meetings

One formal interim analysis meeting will be held to review data related to protocol adherence, treatment efficacy and participant safety. The 3 members of the DMSC will meet when 30-day follow-up data of 366 participants (50% of sample size) have been obtained.

Final analysis meeting

The 3 members of the DMSC will meet when 30-day follow-up data the full sample size (732 participants) have been obtained.

APPENDIX 7: Charter for the independent data monitoring and safety comitee (DMSC)

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure that the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data aggregated by treatment group.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the Steering Committee. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions could be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about protocol adherence and the relative efficacy and safety of interventions. To ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participants, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the Steering Committee.

Closed reports will include analysis of the primary outcome measure and rates of SAEs. These closed reports will be prepared by the study biostatistician, with assistance from the trial data manager and/or principal investigator, in a manner that allow them to remain blinded to group assignment. The closed reports should provide information that is accurate, with follow-up on the primary outcome that is complete as soon as possible and at latest within one month from the date of the DMSC meeting.

APPENDIX 7: Charter for the independent data monitoring and safety comitee (DMSC)

Open reports

For each DMSC meeting, open reports will be available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The DMSC statistician will prepare these open reports in co-operation with the trial data manager and/or principal investigator. The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The IDMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Management Committee

The planned interim analyses will be conducted after participant no. 366 have been followed for 30 days.

After the interim analysis meetings, the DMSC will make a recommendation to the Steering Committee to continue, hold or terminate the trial.

The independent DMSC will recommend pausing or stopping the trial if group-differences in the primary outcome measure or suspected unexpected serious adverse reactions (SUSARs) are observed at the interim analysis with statistical significance levels. If the recommendation is to stop the trial, the DMSC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomized after this interim analysis) or whether a moratorium shall take place (setting the trial at hold) in the further inclusion of participants during these extra analyses. If further analyses of the participants included after the interim analysis is recommended, the rules for finally recommending stopping of the trial should obey the stopping boundary. The DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility will not be an option as an intervention effects less than those estimated in the power calculation for the primary outcome may be clinically relevant as well.

All recommendation will be based on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol. The Steering Committee is jointly responsible with the DMSC for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or change the conduct of the trial made by the DMSC will be considered

and accepted or rejected by the Steering Committee. The Steering Committee will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.
The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.
After completion of the interim analysis, the recommendations from the DMSC and the conclusion reached by the Steering Committee will be submitted to the Ethics Committee.

After completion of the full analysis of primary outcome at day 7 (i.e. PPCs), and secondary outcomes at 30 days, the DMSC will make a recommendation to the Steering Committee to submit a primary report on 7-day and 30-day outcomes.

Statistical monitoring guidelines
The outcome parameters are defined in the statistical analysis plan in the iPROVE-EAL trial protocol. For the two intervention groups, the DMSC will evaluate data on:
- Patients free of PPCs at postoperative day 7th
- Patients free of PPCs at postoperative day 30th

The DMSC will be provided a masked data set (as group 0 and 1) from the coordinating centre. The data set will include data on stratification variables and outcome measures according to the outcomes above in the two groups. Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating center and when to perform the next analysis of the data.
The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Disclosure of Potential Conflicts of Interest and Confidentiality Statement

This form is to be used by DMSC members to declare any conflict of interest with the study to be reviewed.
Members of the Data Monitoring and Safety Committee (DMSC) are selected to reflect the disciplines and medical specialties necessary to interpret data from the study named: iPROVE-EAL
All members of the DMSC are required to be independent of the study being reviewed and all members are required to sign a DMSC Conflict of Interest and Confidentiality statement.
The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsors of the trial or with sponsors having

products that are being evaluated or having products that are competitive with those being evaluated in the trial. Conflict of interest can include personal, professional (in the sense of the trial outcome benefiting the individual professionally), financial or regulatory in nature. The DMSC members will be responsible for advising fellow members of any changes that occur during the course of the trial. Disclosure will serve to protect the integrity of the DMSC and its role in monitoring and oversight of the study and will also help protect the DMSC member from allegations of inappropriate behavior. The DMSC will be responsible for deciding whether those consulting agreements or. financial interests materially impact their objectivity. The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

Confidentiality and Non-Disclosure of Materials and Proceedings

Materials and information made available to the DMSC that are not in the public domain, as well as the discussions that take place during the meetings, are strictly confidential and must not be disclosed to or discussed with anyone who is not a member of the DSMB. Furthermore, confidential information obtained as a DMSC member may not be used by the member for personal benefit or for the benefit of the member's family, associates, or of organizations with which the individual is associated or has a financial involvement.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the MC will appoint the replacement(s).

APPENDIX 7: Charter for the independent data monitoring and safety comitee (DMSC)

DMSC Members Signature Page

Printed name:

Institution:

- I agree to be a part of the Data Monitoring and Safety Committee (DSMC) Board for the iPROVE-EAL study.

- I understand and agree to all the terms and conditions outlined in the DMSC charter for the above named study. I confirm that I am not a part-time or full-time, paid or unpaid employee of any organizations that are involved in the iPROVE-EAL trial. I fully understand the confidential nature of the DMSC process and agree not to disclose or discuss the materials associated with the review or substance of any confidential discussions about the study with any individual not a member of the DMSC or to use the information for my personal benefit or the benefit of others.

- I have no conflicts of interests to disclose that make me ineligible to sit on this committee. I agree that in the event that the above may change during my tenure as a member of the DMSC I will disclose and discuss the risk with the Sponsor/Principal Investigators upon discovery of a risk and sign a new Conflict of Interest and Disclosure Statement form, and will include a description of the conflict. This includes the discovery that an organization with which I am affiliated meets the criteria for a conflict of interest.

Signature:

Date:

APPENDIX 8: Patient Information Sheet (English version)

Title of the study: "**I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial"

Clinicaltrials.gov identificator: NCT04229810
Ethical Research Committee identificator: HCB/2020/0030
Version de protocol: PEAL + IPROVE-EAL. Versión 04.0 data: april-2020
Sponsor: Department of Anesthesia and Critical Care. Hospital Clinic de Barcelona. C/Villaroel, 170. Esc 4. Planta 3. UCI.Q. Teléfono: 932275400
Principal Investigator: Carlos Ferrando Ortolá. Jefe sección UCI Quirúrgica. Departamento de Anestesia y Reanimación. Hospital Clinic de Barcelona. C/Villaroel, 170. Esc 4-planta 3. Teléfono: 932275400/2427.Número de Aprobación Comité de Ética:(VERSIÓN 1.0, julio de 2019)
Hospital: <Inserte nombre del Hospital>
Local Principal Investigator:
Que está siendo llevado a cabo por <Inserte IP local> del Servicio de Anestesiología y Reanimación y que ya ha sido evaluado y aprobado por el Comité de Ética del <Inserte nombre del Hospital>

Dear Patient:
You have been invited to participate in a research study. This consent document contains information that will help you decide if you want to participate. Take your time, read this consent document carefully and ask the doctor or study staff any questions you want. Do not sign this document until you understand all the information presented in the following pages and all your questions about the study have been answered satisfactorily. The study has been evaluated and approved by the Clinical Research Ethics Committee of the Hospital Clinic de Barcelona.

Background:

It is now known from various studies that mechanical ventilation, usually used in patients undergoing general anesthesia to perform a surgical intervention, can itself produce postoperative pulmonary complications in patients with healthy lungs, which worsen the patient's evolution and prognosis.

The causes that justify the appearance of these complications seem to be mainly related to the way the intraoperative mechanical ventilation is applied. In fact, different adjustments and ventilatory strategies such as recruitment maneuvers (strategies to maintain the full volume of the lung), the adjustment of positive pressure at the end of expiration and the maintenance of a certain level of pressure in the airway during the postoperative, have been shown to reduce the incidence of pulmonary and extrapulmonary complications and even mortality.
However, despite knowing their advantages, these strategies are not widely used in routine clinical practice. The reality is that there is a great variability between different doctors and hospitals, in terms of how the adjustment of mechanical ventilation is performed in patients undergoing surgery, and also there are variations in the respiratory management that the patient receives after completing the intervention.
One possible reason for this lack of homogeneity when applying mechanical ventilation is that until now no clinical study has been done to determine which is the best fit and its correlation with the final outcome of the patients. For this reason, the present study is proposed to obtain

the basis to influence the improvement of mechanical ventilation adjustment in the daily clinical practice of the surgical patient during anesthesia and the postoperative period.

What is the purpose of this study?

The objective of the iPROVE-EAL study is to determine whether a customized adjustment of mechanical ventilation for each patient during anesthesia versus a standard ventilatory management (equal for all patients), significantly decreases the occurrence of pulmonary and systemic complications during the first 30 days after surgery, readmissions not scheduled in the intensive care unit, hospital stay as well as in-hospital mortality.

Why have you been asked to participate?

You have been asked to participate in this scientific research study, because you will undergo an emergency laparotomy surgery under general anesthesia and artificial ventilation, and when you leave the operating room it is expected to stay a few hours in the Post-Anesthesia Recovery Unit (PACU). In this study, 732 patients from different hospitals around the world will be included. Because it is not known which of the different adjustments of mechanical ventilation is the best to reduce postoperative pulmonary and systemic complications, it will be assigned randomly (as if we were tossing a coin) to participate in one of the two study groups. Therefore, you have a 50% chance of receiving any of the adjustments.

What does your participation consist of? What type of tests or procedures will be performed?

The start of participation in the study is the day of your surgery. Before starting the study, your personal medical and surgical history and your clinical situation will be reviewed to determine if you meet the criteria to participate in the study. If you meet the criteria and decide to participate, you will be randomly entered into one of the two possible treatment groups:

Group 1: Standard intraoperative and postoperative ventilatory adjustment (the most commonly used for all patients).

Group 2: Customized intraoperative and postoperative ventilatory adjustment.

During the duration of general anesthesia and during admission to the Post-Anesthesia Recovery Unit, data related to the intervention itself and to the manner in which the ventilator settings are scheduled during anesthesia will be collected. Respiratory and circulatory function data will also be recorded by various monitors usually used for this purpose, and by means of the analysis of arterial blood samples.

We will also assess the occurrence of complications of any kind during the 7 days following the intervention, and 30 days after surgery we will be interested to know if you have had any type of complication, if you are still in the hospital or if you have already received the high to your house.

It is possible that other complementary tests could be performed during the study, if indicated (blood test, chest x-ray, electrocardiogram ...). None of these tests is going to be a risk to you. All these determinations will be made by the investigating doctor or the person of the team designated by him.

It is important that you know that your participation in the study does not imply alteration of the treatment you are taking (if you have it) and any treatment that can be done from the clinical-biochemical studies that are performed will always be under medical criteria.

What are the general risks of participating in this study?

APPENDIX 8: Patient Information Sheet (English version)

No risk is anticipated other than usual during any general anesthesia in which open lung maneuvers are applied. The most frequent complication when these maneuvers are applied is a transitory and controlled drop in blood pressure that is treated either by increasing the speed of the liquids administered by the dropper, or with specific medications.

What are the benefits of participating in this study?

Based on previous knowledge and observations it seems that the application of mechanical ventilation in a personalized way can reduce the appearance of postoperative complications, however, we cannot guarantee that you will obtain direct clinical benefits for your participation in the study, since that is precisely what we want to find out. In any case, your participation will help to better understand the outcome of different ventilation strategies and thus improve the prognosis and treatment of future patients.

What will happen if I decide not to participate in this study?

Your participation in this study is totally voluntary. If you decide not to participate in the study, this will not change the treatment and monitoring of your disease done by your doctor or the rest of the caregivers who take care of your illness. Likewise, you may withdraw from the study at any time, without having to give explanations.

Alternative clinical management

The alternative to enter this study is to receive mechanical ventilation with the usual adjustment that may or may not include the maneuvers proposed in this study.

Who can I ask in case of doubt?

It is important that you discuss with any of the investigators of this project the details or doubts that arise before signing the consent for your participation.
Likewise, you can request any explanation that you wish about any aspect of the study and its implications throughout the same by contacting the principal researcher of the center.

Confidentiality:

The data obtained from your participation in the study will be treated according to the national regulation on data protection (Organic Law 15/1999 on the protection of personal data). Your data will be incorporated into a computerized database so that the information obtained cannot be associated with an identified or identifiable person. Equally, in the publication of the results, there won't be any moment in which personal data of patients who have collaborated in this investigation will be leaked.
No data will be accessible to any person who is not part of the team of this study except that the information collected could be reviewed by professionals dependent on the Health Authorities, members of the Clinical Research Ethics Committee, monitor of the study, and other persons designated by the Law to verify that the study is being carried out correctly.
As contemplated by the Law on Protection of Personal Data, you can exercise your right to access, rectify, cancel or oppose your data by contacting the principal investigator of this study.

Other relevant information

APPENDIX 8: Patient Information Sheet (English version)

During your participation in this study, blood samples will be taken from an arterial catheter during the surgical procedure and in the period after the intervention. Part of the blood sample will be analyzed immediately after its extraction and another part will be stored together for its later analysis once the study is finished. What may remain will be eliminated immediately. This sample will always be used for scientific purposes.

Risk for confidentiality

The clinical information obtained in this project will be stored in a database protected by current legislation, under the responsibility of the responsible institutions' investigators. These anonymized data will be kept for future studies, unless you indicate otherwise. The results of this research can be disseminated in journals, medical databases and scientific forums. Personal data that could identify you will never be revealed. The investigators will always have a duty to protect your privacy and maintain all your information confidentially.

Privacy and use of clinical information

The treatment, communication and transfer of your data will be performed according the Regulation (EU) 2016/679 of the European Parliament and the April 27th 2016 Council on Data protection (RGPD). The principal investigator, Dr Carlos Ferrando will be accountable for the custody of the participants' identification codes. As a participant, you may exercise your rights of access, rectification, objection and/or deletion, by contacting any of the principal investigator (telephone number provided at the end of this document). Moreover, you can restrict processing of incorrect data, request a copy of your data or request the transfer of your data to a third party (portability). You may exercise your rights by contacting the principal investigators of the study [Carlos Ferrando (cafeoranestesia@gmail.com)]. We remind you that data cannot be delated even though you cease to take part in the study, in order to guarantee the study's validity and to comply with the legal and medicinal products requirements for authorization. You are entitled to contact the Data Protection Agency if not satisfied. Both the Centre and the Promoter are responsible for data treatment and they commit to meet the data protection regulations in force. Data collected for the study will be identified with a code, so that no information that could identify you is not included. Only your doctor and collaborators will be able to relate your data with you and your clinical history. Therefore, your identity will not be revealed to anyone, except for the healthcare authorities whenever required or in cases of medical emergency. Ethical Committees, healthcare authorities' representatives and authorized personnel will only have access to data in order to perform checks on personal data, on the study procedures and on the compliance with the Good Clinical Practice Standards (always maintaining confidentiality).

The principal investigator and the promoter are obliged to keep all the data collected throughout the study for at least 25 years after the end of the study. After that, your personal data will only be stored at your hospital for your health care. In case we transfer your encoded data outside the EU, to scientific researchers or service providers that collaborate with us, your data will be safeguarded by contracts or other mechanisms recommended by data protection authorities. Further information can be obtained by contacting the Data Protection Delegate (Carlos Ferrando Ortolá, cafeoranestesia@gmail.com).

APPENDIX 8: Patient Information Sheet (English version)

Withdrawal from the study

Even though you have agreed to participate, you may leave the study whenever you wish without any effect on your medical care and without having to offer any explanation. All you need to do is express your intention to the study's principal investigator or his collaborators. If you decide to withdraw from the study, no further data will be collected, while already collected data will be filed.

How can I know the results of the study?

You have the right to know the results of this study, both the general results and those derived from your specific data. You also have the right not to know these results if you wish. For this reason, in the informed consent document, we will ask you which option you prefer. In case you want to know the results, the researcher will send you the results. The overall results of this study will be sent to medical and scientific publications and presented at meetings in the same field for dissemination. The iPROVE-EAL (www.iprove-network.es) website will also provide study data and updated recruitment information, both for patients and for the general public.

What if I have any questions during my participation in the?

In case you have any question or doubt regarding your participation, you can contact the principal investigator at Hospital Clínic de Barcelona (Carlos Ferrando, Chief of the surgical ICU), during working hours (08:000-16:00) or by email to the aforementioned addresses.

Who is organizing and funding this research?

This study is being carried out by a network of doctors from all over the world. The study is coordinated by Dr. Carlos Ferrando. The study is not funded.

Are there economic interests in this study?

Researchers will not receive specific retribution for the dedication to the study (in addition to their usual salary as researchers or doctors). You will not be rewarded for participating. There is no possibility of this study generating benefits in the form of patents.

Who has reviewed this study?

This research study has been reviewed by an independent group of people from a Research Ethics Committee, to protect your safety, your rights, your well-being and your dignity. The Healthcare Ethics Committee of the Hospital Clínic de Barcelona has reviewed the study and has given the approval to carry it out.

What am I supposed to do now?

You must decide if you want to participate in this study. Please, think about what participating in the study involves and talk with your friends and family. The research doctor and the nurse will be happy to answer any questions you may have. When you decide, please inform your doctor. You will be asked to sign a consent form and you will be given a copy that you must keep attached to this information sheet. Please keep these documents. If at any time you have any questions about the study, you can contact the researchers of the iPROVE-EAL study, whose contact information is indicated at the end.

APPENDIX 9: Consent Form (English version)

CONSENT FORM

Study Title: **I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial

I, ... (name and surname of the participant) with ID card……, confirm that:
I have read and understood the information sheet that has been provided.
I have had the opportunity to ask questions and I have received satisfactory answers.

I have talked to: .....(name of the researcher)
I understand that my participation is voluntary.
I understand that I am free to withdraw from the study:

1) at any time
2) without giving any reason
3) without my medical care being affected.

I hearby agree to take part in the study.
Do I want to be informed about the results of the study: yes no (check what applies).
I agree that my medical data may be looked at by individuals from the PEAL Team and I am aware that this consent may be withdrawn at any time. I give my consent to the research team to contact me by telephone 30 days after my surgery.
I have received a signed copy of this Consent Form.

Signature of the patient:

Date:

I have explained the study and its purpose to the patient.
Signature of the researcher:

Date:

ORAL WITNESSED CONSENT FORM

APPENDIX 9: Consent Form (English version)

The declaration of the impartial witness is compulsory when the patient, the father or mother of the patient or the legal representative are incapable of reading or writing.

Study Title: **I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial.

I, ... (name and surname of the participant) with ID card……, confirm that:
I have received the information sheet.
I have had the opportunity to ask questions and I have received satisfactory answers.
I have been provided with adequate information about the study.

I have talked to: .....(name of the researcher)
I hereby declare, under my own responsibility, that: …… (name of the participant) with ID card ……:
Understands that his/her participation is voluntary.
Understands that he/she is free to withdraw from the study:

1) at any time
2) without giving any reason
3) without my medical care being affected.

Has freely expressed his/her agreement to participate in the study.

Signature of the witness Signature of the researcher

Date Date

APPENDIX 9: Consent Form (English version)

LEGAL REPRESENTATIVE CONSENT FORM

Study Title: **I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial

I, ... (name and surname of the legal representative) with ID card…… and as ……..confirm that:
I have read and understood the information sheet that has been provided.
I have had the opportunity to ask questions and I have received satisfactory answers.
I have been provided with adequate information about the study.

I have talked to: ..... (name of the researcher)
I understand that the participation in the study is voluntary.
I understand that it is possible to withdraw from the study:

1) whenever the participant may want to.
2) without giving any reason
3) without the medical care being affected.

In my presence, it has been given to ……..(name of the participant) all the necessary information adapted to his/her level of understanding and agrees to participate in the study. I hereby agree to …… (name of the participant) participating in the study.

Signature of the legal representative Signature of the researcher

Date Date

APPENDIX 10: Patient Information Sheet (Spanish version)

HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio: "**I**ndividualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial"

Identificador en Clinicaltrials.gov: NCT04229810
Número del Comité de Ética: HCB/2020/0030
Versión de protocol: PEAL + IPROVE-EAL. Versión 04.0 data: april-2020
Patrocinador: Department of Anesthesia and Critical Care. Hospital Clinic de Barcelona. C/Villaroel, 170. Esc 4. Planta 3. UCI.Q. Teléfono: 932275400
Investigador Principal del estudio: Carlos Ferrando Ortolá. Jefe sección UCI Quirúrgica. Departamento deAnestesia y Reanimación. Hospital Clinic de Barcelona. C/Villaroel, 170. Esc 4-planta 3. Teléfono: 932275400/2427.Número de Aprobación Comité de Ética:(VERSIÓN 1.0, julio de 2019)
Hospital: <Inserte nombre del Hospital>
Investigador Principal del Hospital:
Que está siendo llevado a cabo por <Inserte IP local> del Servicio de Anestesiología y Reanimación y que ya ha sido evaluado y aprobado por el Comité de Ética del <Inserte nombre del Hospital>

1 INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación, de acuerdo a la legislación vigente, Ley de Investigación Biomédica 14/2007.

Nuestra intención es tan solo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

2 PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

3 DESCRIPCIÓN GENERAL DEL ESTUDIO

Actualmente se conoce por diversos estudios que la ventilación mecánica utilizada habitualmente enlos pacientes que son sometidos a anestesia general para realizar una intervención quirúrgica puede producir por si misma complicaciones pulmonares postoperatorias en pacientes con pulmones sanos, que empeoran la evolución y el

pronóstico del paciente.
El objetivo del estudio iPROVE-EAL es determinar si un ajuste personalizado de la ventilación mecánica para cada paciente durante la anestesia con respecto a un manejo ventilatorio estándar (igual para todos los pacientes), disminuye significativamente la aparición de complicaciones pulmonares y sistémicas durante los primeros 30 días posteriores a la intervención quirúrgica, los reingresos no programados en la unidad de cuidados intensivos, la estancia hospitalaria así como la mortalidad hospitalaria y la mortalidad al año.

Usted ha sido invitado a participar en este estudio, porque va a ser intervenido quirúrgicamente de forma urgente. El estudio iPROVE-EAL es un estudio a nivel internacional, en el que participancentros de todo el mundo, de tipo ensayo clínico de bajo nivel de intervención. En este estudio, se incluirán 732 pacientes de diferentes hospitales europeos. Dado que no se sabe cuál de los diferentes ajustes de la ventilación mecánica es el mejor para disminuir las complicaciones pulmonares y sistémicas postoperatorias, se le asignará de manera aleatoria -al azar- (como si lanzáramos una moneda al aire) para participar en uno de los dos grupos de estudio. Por la tanto tiene una probabilidad del 50% de recibir cualquiera de los ajustes.

El inicio de la participación en el estudio es el día de su intervención quirúrgica. Antes de iniciar el estudio, se revisarán sus antecedentes personales médicos y quirúrgicos, su situación clínica, y los resultados de los últimos análisis realizados para determinar si cumple los criterios para poder participar en el estudio. Si cumple los criterios y decide participar, será introducido de manera aleatoria en uno de los dos grupos de tratamiento posible:

Grupo 1: Ajuste ventilatorio estándar intraoperatorio y postoperatorio (el utilizado más habitualmente para todos los pacientes)
Grupo 2: Ajuste ventilatorio personalizado intraoperatorio y postoperatorio.

Es importante que usted sepa que su participación en el estudio no supone alteración del tratamiento que esté llevando (si lo tiene) y todo tratamiento que se le pueda poner a partir de los estudios clínico-bioquímicos que se le realicen será siempre bajo criterio médico. Tampoco requiere que usted tenga que realizar más visitas al hospital, ni antes ni después de la intervención quirúrgica.

4 BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Basado en conocimientos y observaciones previas parece que la aplicación de la ventilación mecánica de forma personalizada puede reducir la aparición de complicaciones postoperatorias, sin embargo, no podemos garantizar que obtenga beneficios clínicos directos por su participación en el estudio, ya que es precisamente lo que queremos averiguar. En todo caso su participación ayudará a conocer mejor el

resultado de diferentes estrategias de ventilación y así mejorar el pronóstico y el tratamiento de futuros pacientes.

No se prevé ningún riesgo diferente a los habituales durante cualquier anestesia general en la que se aplican maniobras de pulmón abierto. La complicación más frecuente cuando se aplican estas maniobras es la caída de la presión arterial que se trata bien aumentando la velocidad de los líquidos administrados por el gotero, o bien con medicamentos específicos.

5 OBTENCIÓN Y UTILIZACIÓN DE MUESTRAS BIOLÓGICAS

Durante el tiempo que dure la anestesia general y durante su ingreso en la Unidad de Recuperación Postanestésica, se recogerán datos relacionados con la propia intervención y con la forma en que se programen los ajustes del respirador durante la anestesia. También se registrarán datos de función respiratoria y circulatoria por diversos monitores habitualmente empleados para ese fin, y por medio del análisis de muestras de sangre arterial. Estas muestras de sangre arterial serán analizadas inmediatamente tras su extracción y la sangre sobrante del análisis será destruida en el mismo momento. Se valorará además la aparición de complicaciones de cualquier tipo durante los 7 días siguientes a la intervención, y 30 días después de la cirugía nos interesará saber si usted ha tenido algún tipo de complicación, si todavía está en el hospital o si ya ha recibido el alta a su casa. Es posible que pudieran realizarse otras pruebas complementarias durante el estudio, si estuvieran indicadas (analítica de sangre, radiografía de tórax, electrocardiograma...). Ninguna de estas pruebas va a suponer un riesgo para usted. Todas estas determinaciones las realizará el médico investigador o la persona del equipo por él designada.

Se utilizará un código para identificar su muestra y no se utilizará ningún dato suyo que pueda desvelar su identidad. Únicamente el médico del estudio y sus colaboradores podrán relacionar la muestra con usted.

Los datos que se deriven de la utilización de estas muestras se trataran del mismo modo que el resto de datos que se obtengan durante este estudio.

La cesión de muestras biológicas para este estudio es gratuita y voluntaria. Esto supone que usted no tendrá derechos sobre posibles beneficios comerciales de los descubrimientos que pudieran derivarse del resultado de la investigación biomédica.

Si se obtuviera información relevante que pudiera afectar a su salud o a la de sus familiares, se le notificará. En caso que fuera necesario contactar con usted, se utilizarían los datos que constan en su historia clínica. No obstante, se respetará su derecho a decidir que no se le comuniquen éstos, para lo que puede marcar la casilla que se encuentra en el formulario de consentimiento

6 OTRA INFORMACIÓN RELEVANTE

Cualquier nueva información referente al tratamiento utilizado en el estudio y que

pueda afectar a su disposición para participar, que se descubra durante su participación, le será comunicada por su médico lo antes posible.

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos y, puede exigir la destrucción de todas las muestras identificables previamente retenidas para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el promotor y/o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca y se considere relacionado con su participación en el estudio o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio

Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico considere elmás adecuado para su enfermedad.

7 CONFIDENCIALIDAD

La información clínica obtenida en este proyecto será almacenada en una base de datos protegida por la legislación vigente, custodiada bajo la responsabilidad de los investigadores e instituciones responsables. Estos datos, anonimizados, serán conservados para futuros estudios, a no ser que Vd. indique lo contrario. Los resultados de esta investigación se podrán difundir en revistas, bases de datos médicas y foros científicos. Nunca se desvelarán datos personales que pudieran identificarle. Los investigadores siempre tendrán el deber de proteger su privacidad y mantener toda su información de modo confidencial.

El Hospital Clínic de Barcelona, con CIF 0802070C, como responsable del tratamiento de sus datos, leinforma que el tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustará al cumplimiento del Reglamento UE 2016/679 del Parlamento Europeo ydel Consejo de 27 de abril de 2016 relativo a la protección de las personas físicas en cuanto al tratamiento de datos personales y la libre circulación de datos y a la Ley Orgánica 3/2018 de 5 de diciembre de Protección de Datos Personales y Garantía de los derechos digitales.

Los datos recogidos para estos estudios se recogerán identificados únicamente mediante un código, por lo que no se incluirá ningún tipo de información que permita identificar a los participantes. Sólo el médico del estudio y sus colaboradores con un permiso específico podrán relacionar sus datos recogidos en el estudio con su historia clínica.

Su identidad no estará al alcance de ninguna otra persona a excepción de una urgencia médica o requerimiento legal. Podrán tener acceso a su información personal identificada, las autoridades sanitarias, el Comité de Ética de Investigación y personal autorizado por el promotor del estudio, cuando sea necesario para comprobar datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de acuerdo a la legislación vigente.

Sólo se cederán a terceros y a otros países los datos codificados, que en ningún caso contendrán información que pueda identificar al participante directamente (como nombre y apellidos, iniciales, dirección, número de la seguridad social, etc.). En el supuesto de que se produjera esta cesión, sería para la misma finalidad del estudio descrito y garantizando la confidencialidad.

Si se realizara una transferencia de datos codificados fuera de la UE, ya sea a entidades relacionadas con el centro hospitalario donde usted participa, a prestadores de servicios o a investigadores que colaboren con su médico, sus datos quedarán protegidos por salvaguardas como contratos u otros mecanismos establecidos por las autoridades de protección de datos.

Además de los derechos que ya contemplaba la legislación anterior (acceso, modificación, oposición y cancelación de datos, supresión en el nuevo Reglamento) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar estos derechos, o si desea saber más sobre confidencialidad, deberán dirigirse al investigador principal del estudio o al Delegado de Protección de Datos del Hospital Clínic de Barcelona a través de protecciodades@clinic.cat. Asimismo tienen derecho a dirigirse a la Agencia de Protección de Datossi no quedara satisfecho/a. Los datos ya recogidos no se pueden eliminar aunque usted abandone el estudio, para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Pero no se recogerán nuevos datos si usted decide dejar de participar.

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 5 años tras su finalización. Posteriormente, la información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si el paciente hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

8 FINANCIACIÓN

Este estudio se está llevando a cabo por una red de médicos internacional. Es un estudio coordinado por el Dr. Carlos Ferrando. El iPROVE-EAL es un estudio diseñado y

promovido por médicos que no está financiado.
Los investigadores no recibirán retribución específica por la dedicación al estudio (adicional a su salario habitual como investigadores o médicos). Usted no será retribuido por participar. No existe posibilidad de que este estudio genere beneficios en forma de patentes.

APPENDIX 11: Consent Form (Spanish version)

DOCUMENTO DE CONSENTIMIENTO INFORMADO

Título del PROYECTO:

Complicaciones pulmonares postoperatorias en cirugía abdominal urgente. Incidencia, factores de riesgo y estrategias de ventilación pulmonar protectoras personalizadas.

Yo, ... (nombre y apellidos del participante) con DNI……, He leído el documento de información que se me ha entregado.
He podido hacer preguntas sobre el estudio y he recibido suficiente información sobre el mismo.
He hablado con: .....(nombre del investigador)
Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:
1) cuando quiera
2) sin tener que dar explicaciones
3) sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el estudio
Deseo ser informado sobre los resultados del estudio: sí no (marque lo que proceda)
Doy mi conformidad para que mis datos clínicos sean revisados por personal ajeno al centro, para los fines del estudio, y soy consciente de que este consentimiento es revocable.
He recibido una copia firmada de este Consentimiento Informado.

Firma del participante:

Fecha:

He explicado la naturaleza y el propósito del estudio al paciente mencionado

Firma del Investigador:

Fecha:

APPENDIX 11: Consent Form (Spanish version)

CONSENTIMIENTO ORAL ANTE TESTIGOS

La declaración del testigo imparcial es obligatoria cuando el paciente, el padre o madre, el tutor o el representante legal no sepan leer o escribir.

Título del PROYECTO:

Complicaciones pulmonares postoperatorias en cirugía abdominal urgente. Incidencia, factores de riesgo y estrategias de ventilación pulmonar protectoras personalizadas.

Yo,..... (nombre y apellidos) con DNI……, He recibido la hoja de información sobre el estudio.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He sido informado por: ..... (nombre del investigador)
Declaro bajo mi responsabilidad que: .....
(nombre del participante del ensayo) con DNI……..
Comprende que su participación es voluntaria.

Comprende que puede retirarse del estudio:
1. Cuando quiera
2. Sin tener que dar explicaciones.
3. Sin que esto repercuta en mis cuidados médicos.

Y ha expresado libremente su conformidad para participar en el estudio.

Firma del Testigo Firma del Investigador

Fecha Fecha

APPENDIX 11: Consent Form (Spanish version)

CONSENTIMIENTO DEL REPRESENTANTE LEGAL

Título del PROYECTO:

Complicaciones pulmonares postoperatorias en cirugía abdominal urgente. Incidencia, factores de riesgo y estrategias de ventilación pulmonar protectoras personalizadas.

Yo, ... (nombre y apellidos del representante) con DNI…… y en calidad de…….
He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He hablado con: ..... (nombre del Investigador)
Comprendo que la participación en el estudio es voluntaria
Comprendo que es posible retirarse del estudio:
1. Cuando así lo quiera el participante
2. Sin tener que dar explicaciones.
3. Sin que esto repercuta en sus cuidados médicos.
En mi presencia se ha dado a ..... (nombre del participante), toda la información pertinente adaptada a su nivel de entendimiento y está de acuerdo en participar.
Y presto mi conformidad con que ..... (nombre del participante) participe en el estudio.

Firma del Representante
Firma del Investigador

Fecha Fecha

APPENDIX 12: iPROVE-EAL Case Report Form (CRF)

iPROVE-EAL

Individualized **P**eriope**R**ative **O**pen lung **VE**ntilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial

Identifier	
HOSPITAL	
PATIENT IDENTIFICATION	
RESEARCHER 1	
RESEARCHER 2	

CASE REPORT FORM (CRF)
Version 01.0 05-08-2019

CONFIDENCIAL

HOSPITAL		SUBJECT	

PREOPERATIVE DATA

DEMOGRAPHIC DATA		
Age (years):	☐ Male ☐ Female	Heigth(cm):
weight (kg):	IMC (kg/m^2):	Ideal body weight (kg/m^2):
Admission date (dd/mm/yyyy):	Surgery date (dd/mm/yyyy):	Date of hospital discharge (dd/mm/yyyy):

Inclusion criteria	YES	NO
Age equal to or older than 18 years	☐	☐
Emergency laparo-tomy/scopy	☐	☐
Informed consent	☐	☐

Exclusion criteria	YES	NO
Pregnancy or lactation	☐	☐
Participation on another RCT with similar intervention or outcome	☐	☐
Moderate or severe ARDS	☐	☐
Mechanical ventilation on the last 15 days due to acute or chronic pathology	☐	☐
Diagnosed or suspected intracraneal hypertension (> 15 mmHg)	☐	☐
Pnneumothorax or giant bullae on chest X-ray or CT	☐	☐
Refractary shock	☐	☐

Informed Consent

☐ **No Specify the reason:**

☐ Rejected by patient or relatives ☐ Rejected by the physician ☐ Absence of investigator

☐ **Yes Indicate date/time of getting the informed consent.**

____/____/____ (dd/mm/yyyy) hour_____:____

HOSPITAL		SUBJECT	

CO-MORBIDITIES	YES	NO	CO-MORBIDITIES	YES	SI
Arterial hypertension	☐	☐	Dyslipemia	☐	☐
Ischemic cardiopathy	☐	☐	OSA	☐	☐
Diabetes mellitus II	☐	☐	COPD	☐	☐
smoker	☐	☐	Chronic renal failure	☐	☐
Ex smoker (> 3 months)	☐	☐	Chronic liver failure	☐	☐
Alcohol consumption (more than two drinks per day)	☐	☐	Oncological	☐	☐
Neuromuscular disease	☐	☐	Inmunosuppresion	☐	☐

Surgery	
☐ **Laparotomy**	☐ **Laparoscopy**
☐ Mesenteric ischemia	☐ Anastomotic leak
☐ Hemoperitoneum	☐ Adhesiolisis
☐ Colorectal resection	☐ Small bowel resection
☐ Gastrectomy	☐ Grastrointestinal perforation
☐ Hemoperitoneum (Abdominal, urological, gynecological)	☐ Cholecystectomy
☐ Exploratory laparotomy	☐ Hepatic transplant
☐ Vascular (Aneurysmal surgeries)	☐ Urological other
☐ Hepatic transplantation	☐ Kidney transplantation

PREOPERATIVE DATA			
Primary diagnosis:			
ASA ☐ I ☐ II ☐ III ☐ IV			
ARISCAT ☐ Moderate (26-44 points) ☐ severe (> 44 points)			
SpO_2 (FIO_2 0.21)	**%**	**Preoperative Hb (g/dl)**	
Lung infection on the last month ☐ yes ☐ No			
Clinical Frailty Scale (from 1 to 9):		**Charlson:**	

HOSPITAL		SUBJECT	

INTRAOPERATIVE DATA

NOTE: It is mandatory to ask for /obtain the informed consent **before** randomization.

Data should be reported also for the non-randomized patients.

RANDOMIZATION		
☐ No	☐ **Negative Air-Test**	☐ **Other reason**
☐ Yes	**Date and time:** **___/___/_____ and ____:____**	☐ **STD-O2** ☐ **iOLA-iHFNC**

**Only if arterial catheterization*

INTRAOPERATIVE DATA			
VARIABLE	**T0** (10 min after intuabtion)	**T1** (60 min after intubation)	**T2** (pre-extubabion)
PEEP (cmH_2O)			
RR			
VT (ml)			
FiO_2 (%)			
***PaO_2 (mmHg)**			
***PaO_2/FiO_2 (mmHg)**			
***$PaCO_2$ (mmHg)**			
***pH**			
Peak pressure (cmH_2O)			
Plateau pressure (cmH_2O)			
Cdyn (ml/cmH_2O)			
Raw (ml/cmH_2O)			
PAM (mmHg)			
IC ($ml/min/m^2$)			
Air-Test (0.21 FiO_2 during 5 min or SpO_2 97%)			
SpO_2 (%) a FiO_2 21%			

Fluids (ml)			
Fluids		Red blood cells	
Estimated blood loss		Urinary output	
Additional information			
Duration of surgery (min)		Duration of MV (min)	
Surgical position. Supine☐ Trend ☐ Reverse trend ☐			

HOSPITAL		SUBJECT	

Use of vasoactive drugs ☐ Yes No ☐ Drug/dose:	**Pneumoperitoneum pressure. (mmHg):**

Anesthetic management	
Hypnotic manteinance ☐ Intravenous ☐ Halogenated	**Antibiotic prophylaxis.** Yes ☐ No ☐
Neuromuscular blockade Yes ☐ No ☐	**Epidural Analgesia** Yes ☐ No ☐
Quantitative Neuromusc Monitorization Yes ☐ No ☐	**Temperature monitoring** Yes ☐ No ☐
NMB reversion Yes ☐ No ☐	**Depth of anesthesia monitoring** Yes ☐ No ☐
TOFr >0,9 before extubation Yes ☐ No ☐	

Open lung approach				
*First RM **only if** positive air-test after induction* *(SpO2 < 97% while breathing room air))*				
First alveolar recruitment maneuver (RM)	**Opening pressure**	**OL-PEEP**	**Cdyn**	**SpO2 (FIO2 21%) 5 min after the OL-PEEP**
Following RM **only if** **SpO2 < 97% while breathing room air + a drop in Cdyn > 10%**				
60 minutes ☐ YES ☐ No,				
120 minutes ☐ YES ☐ No,				
180 minutes ☐ YES ☐ No,				
240 minutes ☐ YES ☐ No,				
300 minutes ☐ YES ☐ No,				
360 minutes ☐ YES ☐ No,				

RM DUE TO INCIDENTAL DISCONNECTION			
☐ Yes ☐ No	If yes, indicate the number of RM:		
RM failure			
First RM	☐ Yes ☐ No	After ephedrine/phenylephrine administration	☐ Yes ☐ No
Followings RM	☐ Yes ☐ No	After ephedrine/phenylephrine administration	☐ Yes ☐ No
Intraoperative Rescue maneuvers (See protocol criteria)			
☐ Yes ☐ No			

HOSPITAL		SUBJECT	

POSTOPERATIVE DATA

POSTOPERATIVE DATA		
High-flow nasal cannula (iOLA-iHFNC group) (Only if SpO_2 <97% (FIO_2 0.21)		
☐ Yes ☐ No		
Postoperative rescue maneuvers (see protocol criteria)		
☐ Yes ☐ No If yes, indicate: ☐ NIMV ☐ IMV		
Extubated patient in the OR		
☐ Yes ☐ No If not, indicate: ☐ Respiratory ☐ Hemodynamic ☐ Neurological ☐ Other: :		
MV time until extubation (min)		
Postoperative management according to protocol?		
☐ Yes ☐ No If not, indicate:		
* (In case of no intraoperative extubation data from days 0, 1 and 3 will be collected after extubation. Data from days 7 and 30 (primary and secondary outcome) will be collected from the day of surgery)		
Analgesic management		
Drug		
☐ Morfine ☐ Fentanil ☐ If Other, specify which:		
Epidural		
☐ Yes ☐ No		
Paravertebral		
☐ Yes ☐ No		
VAS (VAS evaluation will be done prior to the diagnose of atelectasis/hypoxemia)		
Minutes after surgery	VAS	Rescue with morphine or derivates?
15-30		☐ Yes ☐ No

NOTE: Before the Air-Test a VAS < 4 must be guaranteed

Air Test after 15-30 min at PACU	SpO2: %

HOSPITAL		SUBJECT	

SAEs It is considered a SAE when it appears directly related with RM The local principal investigator must inform the coordinating center during the first 24h
Hemodynamic shock. ☐ Yes ☐ No
Arrhymia with hemodynamic inestability. ☐ Yes ☐ No
Pneumothorax. ☐ Yes ☐ No
Cardiorespiratory arrest ☐ Yes ☐ No

PROTOCOL NON FULFILLMENT
INTRAOPERATIVE
Related to the specific ventilatory protocol
☐ **Yes** ☐ No
If yes, specify which:
Related to the RM
☐ **Yes** ☐ No
If yes, specify which:
POSTOPERATIVE
Related with the air-test
☐ **Yes** ☐ No
If yes, specify which:
Related with the HFNT
☐ **Yes** ☐ No
If yes, specify which:
Related with the rescue maneuvers
☐ **Yes** ☐ No

HOSPITAL		SUBJECT	

If yes, specify which:
Observations

HOSPITAL		SUBJECT	

POSTOPERATIVE DATA
Acute postoperative respiratory failure at PACU
Yes ☐ No ☐ If yes, indicate treatment: ☐ Increase in FIO_2 ☐ HFNT ☐ CPAP ☐ NIMV ☐ IMV
Was the patient extubated in the OR•
Yes ☐ No ☐ If not, indicate: ☐ Respiratory ☐ Hemodynamic ☐ Neurological ☐ Others:
¿ICU due to MV requirement? Yes ☐ No ☐ If yes, indicate: Time until extubation (min):

6h postoperative arterial blood gas analysis			
SpO_2		PaO_2 (mmHg)	
FIO_2		PaO_2/FIO_2 (mmHg)	
$PaCO_2$ (mmHg)		pH	
SpO_2 (FiO_2 21%)			

OUTCOMES

Day 0		
Does the patient have any pulmonary complication BEFORE surgery? ☐ Yes ☐ No		
☐ Mild acute respiratory failure	☐ Severe acute respiratory failure	☐ Weaning failure
☐ARDS mild. ☐ ARDS moderate. ☐ ARDS severe	☐ Respiratory infection	☐ Pleural effusion
☐ Atelectasis	☐ Pneumothorax	☐ Bronchoespasm
☐ Aspiration pneumonitis	☐ Pulmonary edema	☐ Pulmonary embolism
Imaging technique:		
☐ Chest X-ray	☐ LUS	☐ CT
Does the patient have any systemic complication? ☐ Yes ☐ No		
☐ Yes ☐ No		
☐ Surgical site infection	☐ Urinary infection	
☐ Septic shock. ☐ Sepsis	☐ AKI I ☐ AKI II ☐ AKI III	
☐ Cardiac failure	☐ Myocardial ischemia	

HOSPITAL		SUBJECT	

□ De novo Arrythmia	□ Delirium
□ Multiorgan failure	□ Paralytic ileus
□ Postoperative hemorrhage	□ Anastomotic leakage

Day 1

Does the patient have any pulmonary complication until the first day after surgery? □ Yes □ No

□ Mild acute respiratory failure	□ Severe acute respiratory failure	□ Weaning failure
□ARDS mild. □ ARDS moderate. □ ARDS severe	□ Respiratory infection	□ Pleural effusion
□ Atelectasis	□ Pneumothorax	□ Bronchoespasm
□ Aspiration pneumonitis	□ Pulmonary edema	□ Pulmonary embolism

Imaging technique:

□ Chest X-ray	□ LUS	□ CT

Does the patient have any systemic complication? □ Yes □ No

□ Yes □ No

□ Surgical site infection	□ Urinary infection
□ Septic shock. □ Sepsis	□ AKI I □ AKI II □ AKI III
□ Cardiac failure	□ Myocardial ischemia
□ De novo Arrythmia	□ Delirium
□ Multiorgan failure	□ Paralytic ileus
□ Postoperative hemorrhage	□ Anastomotic leakage

ICU admission? □ Yes □ No

□ Yes □ No

□ Per protocol	□ Respiratory
□ Septic shock. □ Sepsis	□ Multiorgan failure
□ Renal failure	□ Hemodynamic failure
□ Others:	ICU length of stay (hours):

Re-intervention □ Yes □ No

☐ Bleeding	☐ Anastomotic leakage
☐ Infection	☐ Others:

OUTCOMES

Day 3		
Does the patient have any pulmonary complication until the first day after surgery? ☐ Yes ☐ No		
☐ Mild acute respiratory failure	☐ Severe acute respiratory failure	☐ Weaning failure
☐ARDS mild. ☐ ARDS moderate. ☐ ARDS severe	☐ Respiratory infection	☐ Pleural effusion
☐ Atelectasis	☐ Pneumothorax	☐ Bronchoespasm
☐ Aspiration pneumonitis	☐ Pulmonary edema	☐ Pulmonary embolism
Imaging technique:		
☐ Chest X-ray	☐ LUS	☐ CT
Does the patient have any systemic complication? ☐ Yes ☐ No		
☐ Surgical site infection	☐ Urinary infection	
☐ Septic shock. ☐ Sepsis	☐ AKI I ☐ AKI II ☐ AKI III	
☐ Cardiac failure	☐ Myocardial ischemia	
☐ De novo Arrythmia	☐ Delirium	
☐ Multiorgan failure	☐ Paralytic ileus	
☐ Postoperative hemorrhage	☐ Anastomotic leakage	
ICU admission? ☐ Yes ☐ No		
☐ Per protocol	☐ Respiratory	
☐ Septic shock. ☐ Sepsis	☐ Multiorgan failure	
☐ Renal Failure	☐ Hemodynamic failure	
☐ Others:	ICU length of stay (hours):	
Re-intervention ☐ Yes ☐ No		
☐ Bleeding	☐ Anastomotic leakage	

HOSPITAL		SUBJECT	

☐ Infection	☐ Others:

OUTCOMES

Day 5		
Does the patient have any pulmonary complication until the first day after surgery? ☐ Yes ☐ No		
☐ Mild acute respiratory failure	☐ Severe acute respiratory failure	☐ Weaning failure
☐ARDS mild. ☐ ARDS moderate. ☐ ARDS severe	☐ Respiratory infection	☐ Pleural effusion
☐ Atelectasis	☐ Pneumothorax	☐ Bronchoespasm
☐ Aspiration pneumonitis	☐ Pulmonary edema	☐ Pulmonary embolism
Imaging technique:		
☐ Chest X-ray	☐ LUS	☐ CT

Does the patient have any systemic complication? ☐ Yes ☐ No	
☐ Surgical site infection	☐ Urinary infection
☐ Septic shock. ☐ Sepsis	☐ AKI I ☐ AKI II ☐ AKI III
☐ Cardiac failure	☐ Myocardial ischemia
☐ De novo Arrythmia	☐ Delirium
☐ Multiorgan failure	☐ Paralytic ileus
☐ Postoperative hemorrhage	☐ Anastomotic leakage
ICU admission? ☐ Yes ☐ No	
☐ Per protocol	☐ Respiratory
☐ Septic shock. ☐ Sepsis	☐ Multiorgan failure
☐ Renal Failure	☐ Hemodynamic failure
☐ Others:	ICU length of stay (hours):
Re-intervention ☐ Yes ☐ No	
☐ Bleeding	☐ Anastomotic leakage
☐ Infection	☐ Others:

HOSPITAL		SUBJECT	

OUTCOMES

Day 7		
Does the patient have any pulmonary complication until the first day after surgery? ☐ Yes ☐ No		
☐ Mild acute respiratory failure	☐ Severe acute respiratory failure	☐ Weaning failure
☐ARDS mild. ☐ ARDS moderate. ☐ ARDS severe	☐ Respiratory infection	☐ Pleural effusion
☐ Atelectasis	☐ Pneumothorax	☐ Bronchoespasm
☐ Aspiration pneumonitis	☐ Pulmonary edema	☐ Pulmonary embolism
Imaging technique:		
☐ Chest X-ray	☐ LUS	☐ CT
Does the patient have any systemic complication? ☐ Yes ☐ No		
☐ Surgical site infection	☐ Urinary infection	
☐ Septic shock. ☐ Sepsis	☐ AKI I ☐ AKI II ☐ AKI III	
☐ Cardiac failure	☐ Myocardial ischemia	
☐ De novo Arrythmia	☐ Delirium	
☐ Multiorgan failure	☐ Paralytic ileus	
☐ Postoperative hemorrhage	☐ Anastomotic leakage	
ICU admission? ☐ Yes ☐ No		
☐ Per protocol	☐ Respiratory	
☐ Septic shock. ☐ Sepsis	☐ Multiorgan failure	
☐ Renal failure	☐ Hemodynamic failure	
☐ Others:	ICU length of stay (hours):	
Re-intervention ☐ Yes ☐ No		
☐ Bleeding	☐ Anastomotic leakage	
☐ Infection	☐ Others:	

HOSPITAL		SUBJECT	

OUTCOMES

Day 30		
Does the patient have any pulmonary complication until the first day after surgery? ☐ Yes ☐ No		
☐ Mild acute respiratory failure	☐ Severe acute respiratory failure	☐ Weaning failure
☐ARDS mild. ☐ ARDS moderate. ☐ ARDS severe	☐ Respiratory infection	☐ Pleural effusion
☐ Atelectasis	☐ Pneumothorax	☐ Bronchoespasm
☐ Aspiration pneumonitis	☐ Pulmonary edema	☐ Pulmonary embolism
Imaging technique:		
☐ Chest X-ray	☐ LUS	☐ CT
Does the patient have any systemic complication? ☐ Yes ☐ No		
☐ Surgical site infection	☐ Urinary infection	
☐ Septic shock. ☐ Sepsis	☐ AKI I ☐ AKI II ☐ AKI III	
☐ Cardiac failure	☐ Myocardial ischemia	
☐ De novo Arrythmia	☐ Delirium	
☐ Multiorgan failure	☐ Paralytic ileus	
☐ Postoperative hemorrhage	☐ Anastomotic leakage	
ICU admission? ☐ Yes ☐ No		
☐ Per protocol	☐ Respiratory	
☐ Septic shock. ☐ Sepsis	☐ Multiorgan failure	
☐ Renal failure	☐ Hemodynamic failure	
☐ Others:	ICU length of stay (hours):	
Re-intervention ☐ Yes ☐ No		
☐ Bleeding	☐ Anastomotic leakage	
☐ Infection	☐ Others:	
Clinical Frailty Scale (from 1 to 9):		

HOSPITAL		*SUBJECT*	

Was the patient excluded from the study?
☐ Yes ☐ No
If yes, indicate the cause
☐ The patient revoked his consent
☐ The surgical intervention is not performed
☐ The patient meets some exclusion criteria

Survival	**Alive**	**Death**
Status at 7 days post-surgery	☐	☐
Status at 30 days post-surgery	☐	☐
Status at 365 days post-surgery	☐	☐

Signed (Local investigator):

Name and family name: Data:

NOTE:

At the end of the study, a copy of the CRF will be collected on paper completed and signed by the Investigator.

	APPENDIX 13: SERIOUS ADVERSE EVENT NOTIFICATION	STUDY ID: iPROVE-EAL	SPONSOR: Department of Anesthesiology and Critical Care. Hospital Clinic de Barcelona

La notificación y definiciones de efectos adversos se justa a la legislación española (Real Decreto 1090/2015).

PATIENT INFORMATION			
STUDY ID	**Gender**	**Weight**	**Height**

ADVERSE EVENT INFORMATION		
Event term (grouping symptoms as a single disease)	**Type of notification**	**Data and time of the event**
Event´s description (state before onset, course of AE indicating significant findings, laboratory data, measurements taken, etc.)		
Seriousness ☐ Death ☐ Life in danger ☐ Congenital anomaly ☐ Hospitalization ☐ Permanent / significant disability ☐ Another major medical condition		
Intensity: ☐ Severe ☐ Moderate ☐ Mild		
Result: ☐ Solved ☐ Non Solved ☐ Unknown ☐ Solved with con sequels ☐ Fatal Data:		

INFORMATION METHODOLOGY IN RESEARCH	
IMP	**Relationship to the adverse event**
	☐ True ☐ Probable ☐ Possible ☐ Unlikely ☐ Not related ☐ Unclassifiable ☐ Not classified
START DATE:	**END DATE:**

RESEARCHER INFORMATION				
Principal investigator	**Center**	**Reported by (researcher)**	**Data**	**Signature**

APPENDIX 14: PATIENT REGISTRATION iPROVE-EAL

HOSPITAL PATIENT REGISTRATION. iPROVE-EAL	
STUDY ID: iPROVE-EAL SPONSOR: Department of Anesthesia and Critical Care. Hospital Clinic of Barcelona	CENTER: LOCAL IP:

It is the investigator's obligation to keep this document in custody.

Number	Subject identification	Anonymized code

APPENDIX 14: PATIENT REGISTRATION iPROVE-EAL
