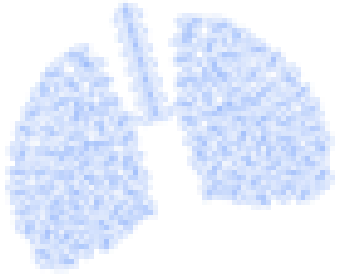
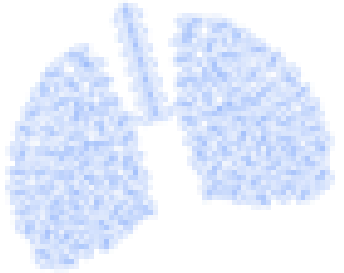


Title:

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.

iPROVE-EAL Trial

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



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

1.4 Study Sponsor:

Anesthesiology and Critical Care Department.

Hospital Clínic de Barcelona

C/Villarroel, 170. Barcelona. 08036

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1.6 Study Methodology:

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1.7 Coordinating and Study monitoring:

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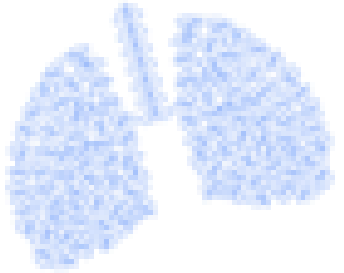
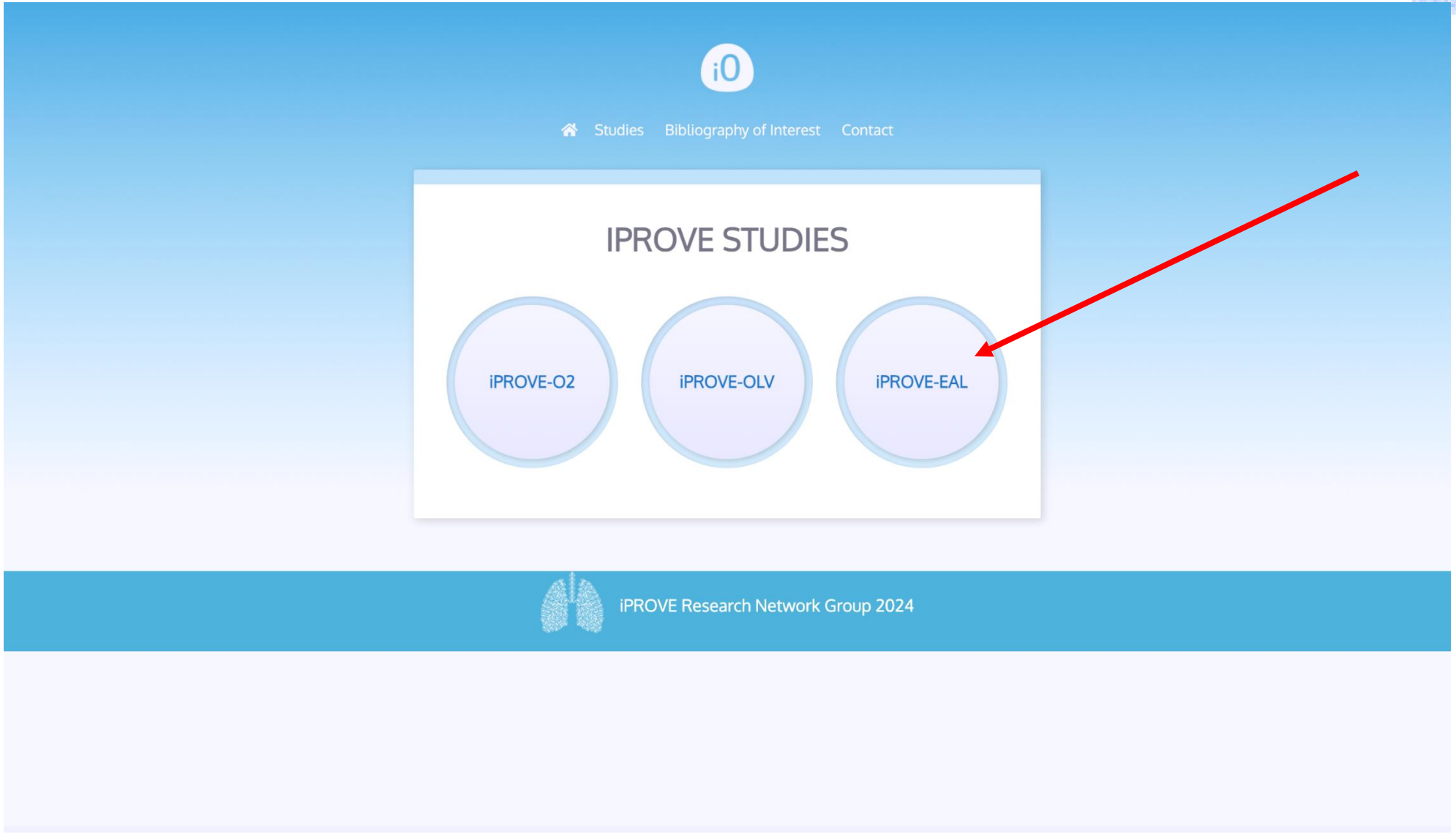


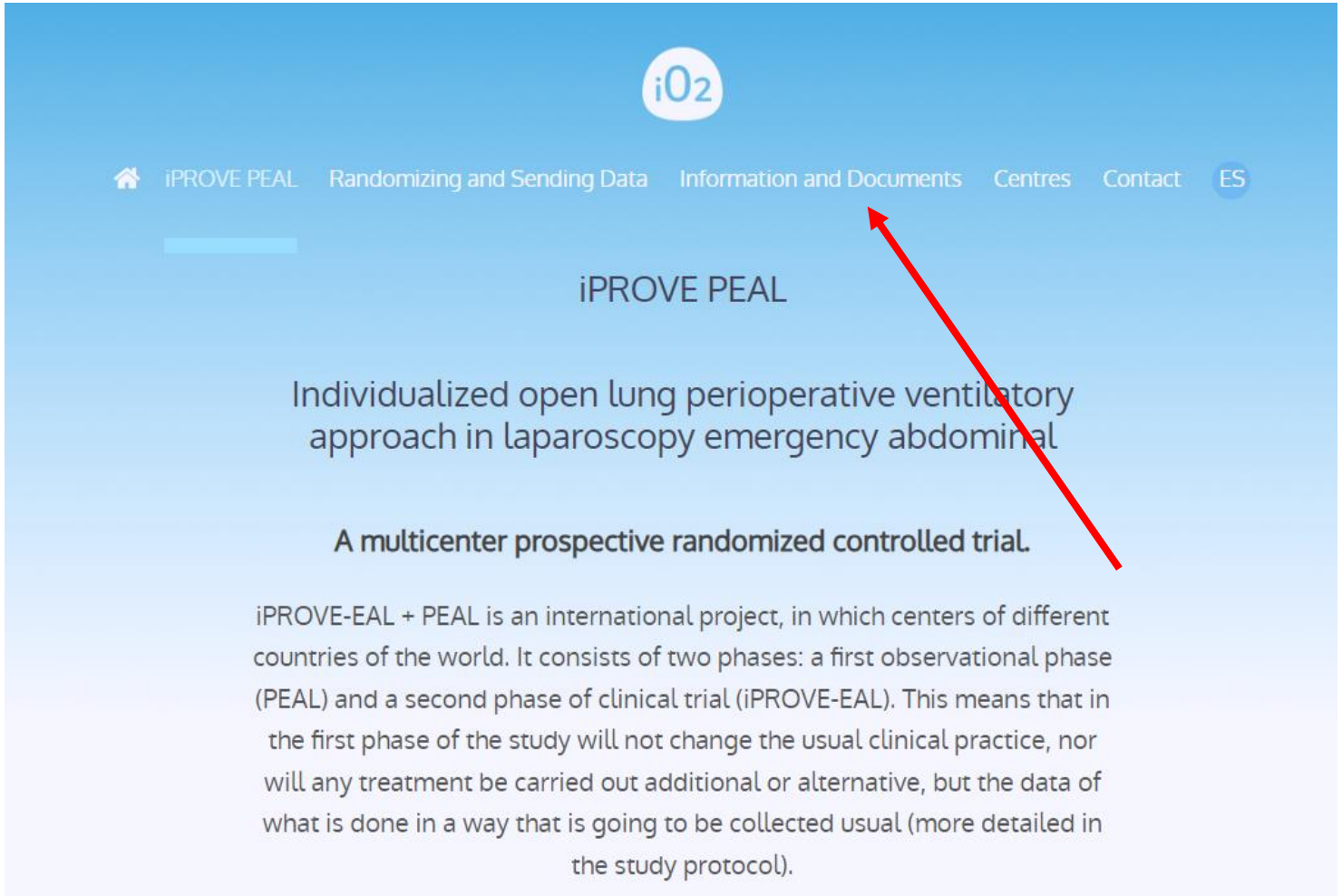
Website: iprove-network.es

Contact information: iprove.eal@gmail.com

Website: iprove-network.es

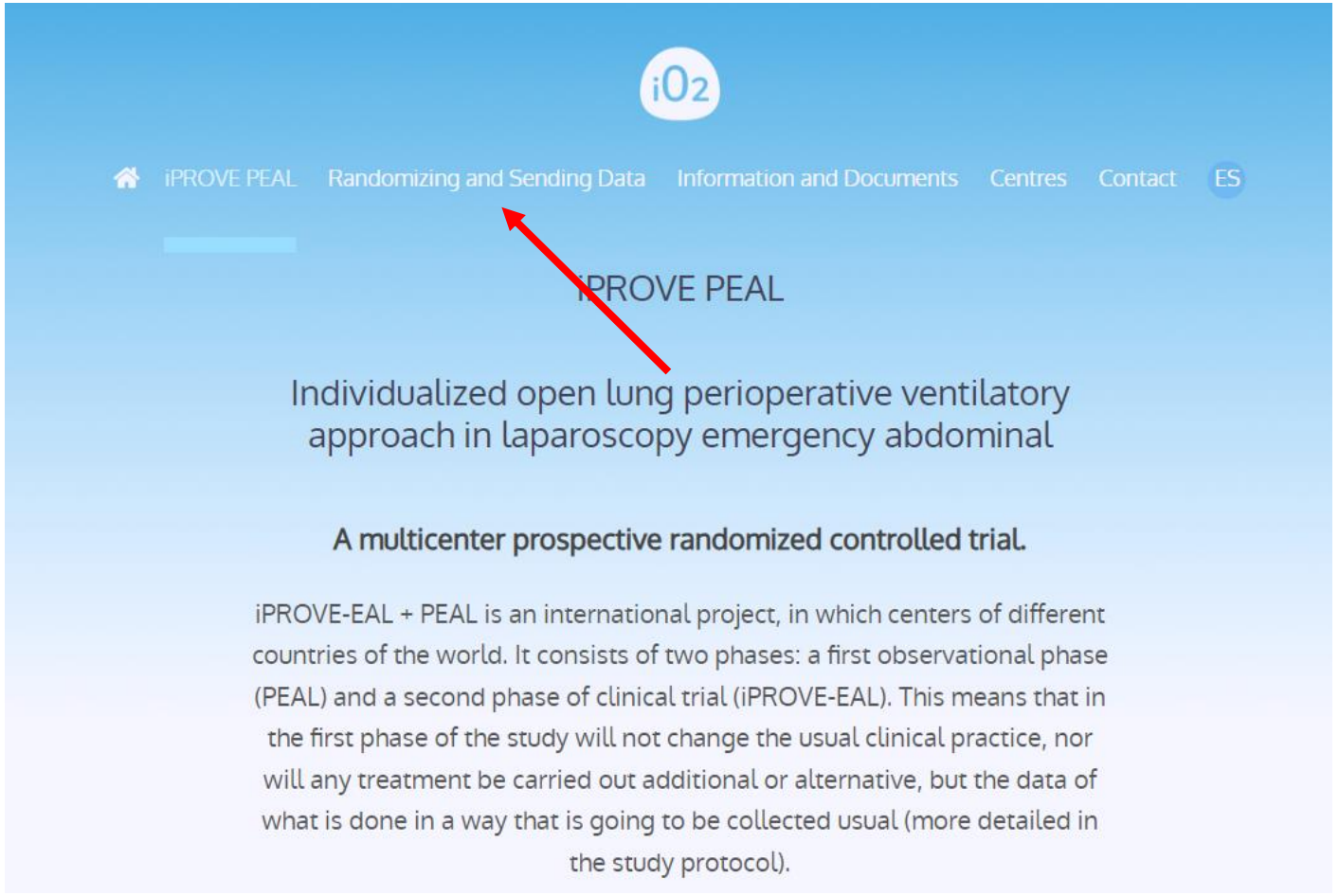


Website: iprove-network.es

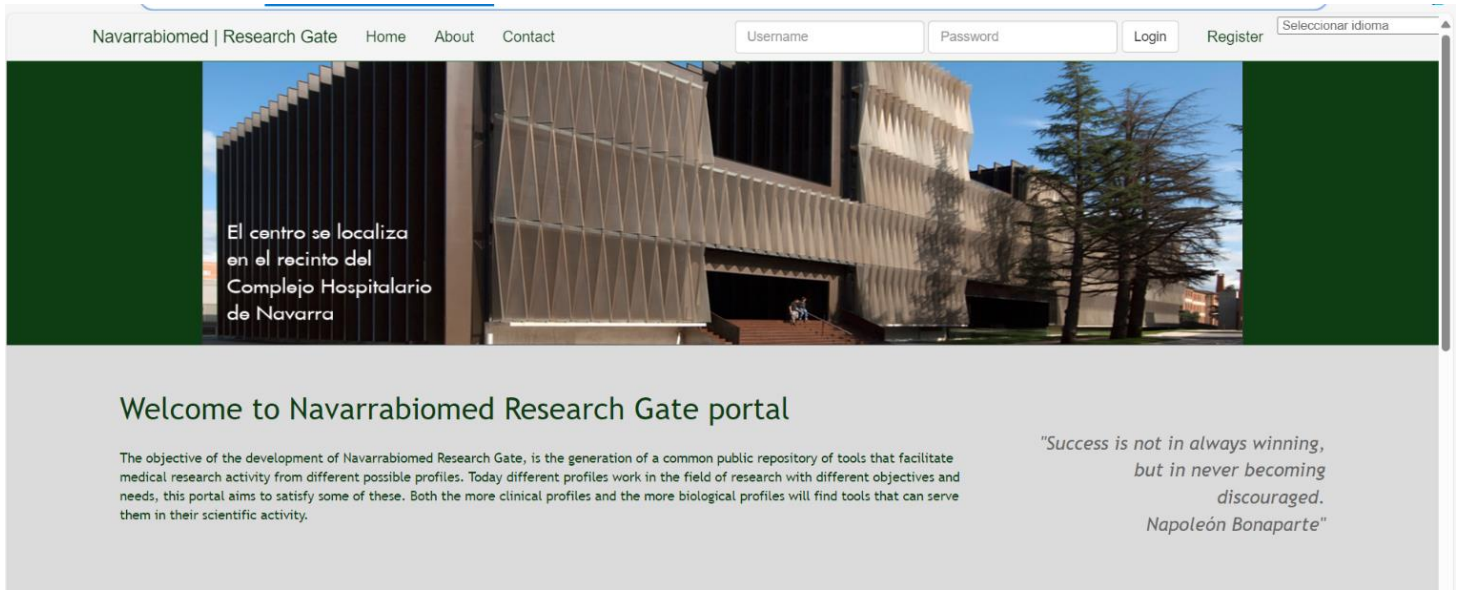


1.- Protocol
2.- CRF
3.- Investigator information brochure
4.- Ethical Committee approval
5.- Patient registration
6.- SAEs
7.- Patient information sheet
8.- Informed consent
9.- Printable cards

Access to the eCRF and randomization website

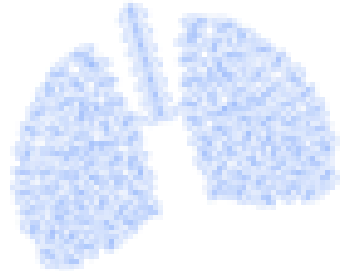


Website: http://www.navarrabiomed-researchgate.com/



- Enter or modify data in eCRF
- Patient randomization

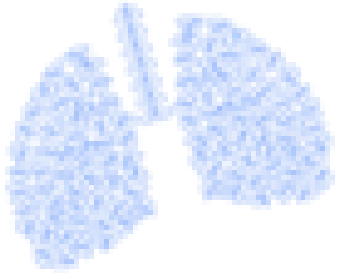
Registration and contact form in order to access to eCRF (more details in appendix 3 Investigator brochure)



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. At the end of the study some of these data will be requested for the CONSORT Flowchart

Number	Subject identification	Subjetc included* (Y or N)	Subject randomized** (Y or N)	Anonymized code

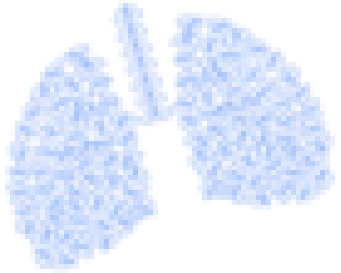


Design

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

Objectives

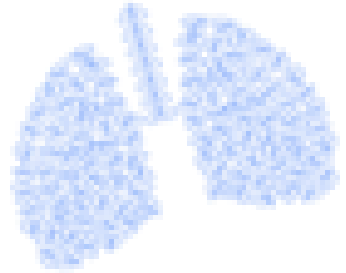
A randomized clinical trial that compares an individualized and monitored perioperative open lung ventilation strategy versus a conventional standardized lung protective ventilation in patients undergoing emergency abdominal surgery with clinical signs of lung collapse.



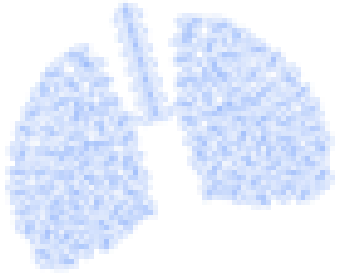
Inclusion criteria:

- adult men and women ≥18 years of age who underwent emergency abdominal surgery and sign the informed consent.
- 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.

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



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



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.

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.

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.

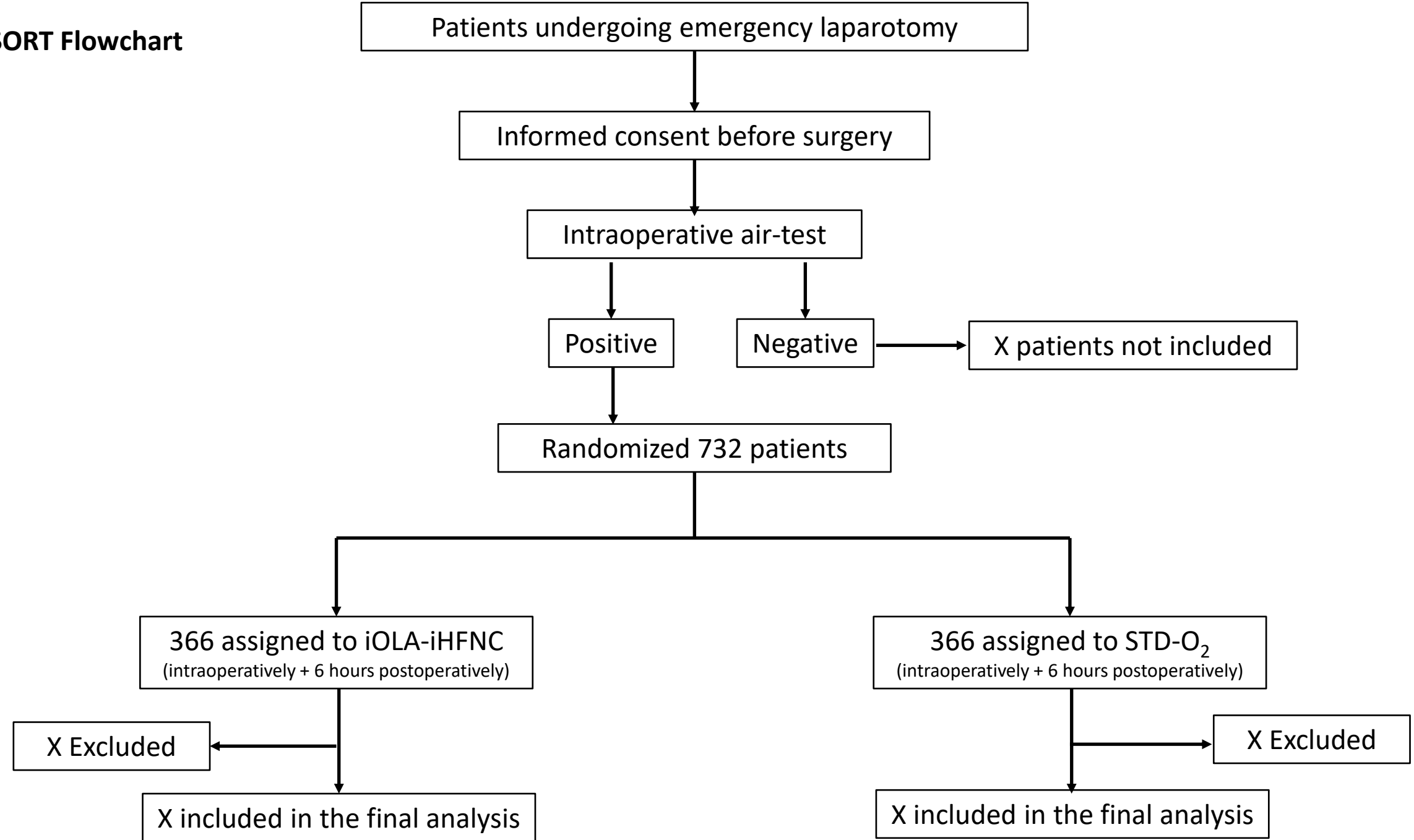
- Postoperative non-pulmonary complications during the first 7 postoperative days and between days 7 and 30 after the intervention. They include: 1) Cardiac ischemia, 2) de novo arrhythmia, 3) Heart failure, 4) Sepsis, 5) Septic shock, 5) Acute renal failure, 6) Surgical wound infection, 7) Urinary infection,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

Standard definition criteria for all postoperative complications are described in the protocol and in the investigator information brochure

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

CONSORT Flowchart



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 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.

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

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)

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

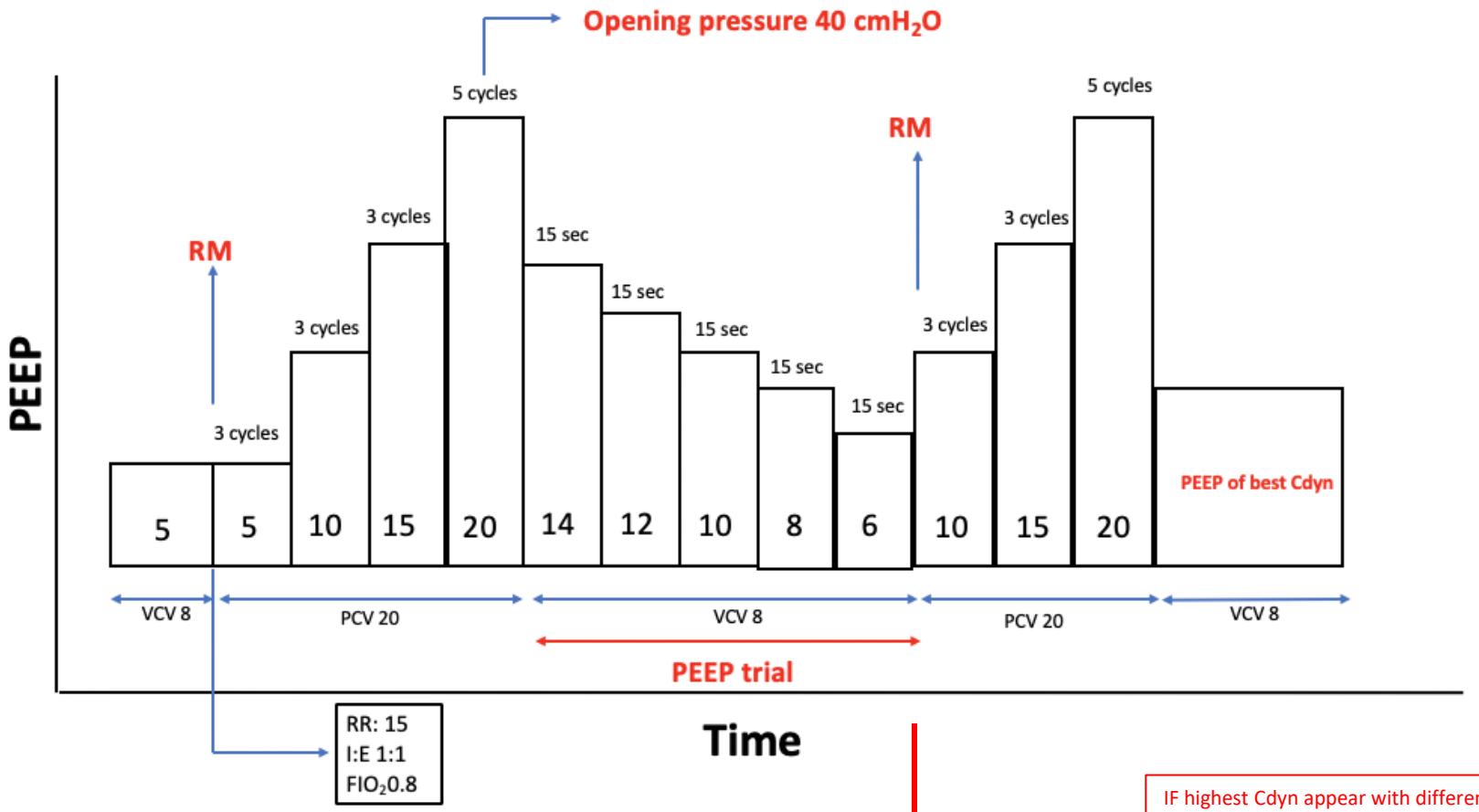
RECRUITMENT MANEUVER A + PEEP SETTING A

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.

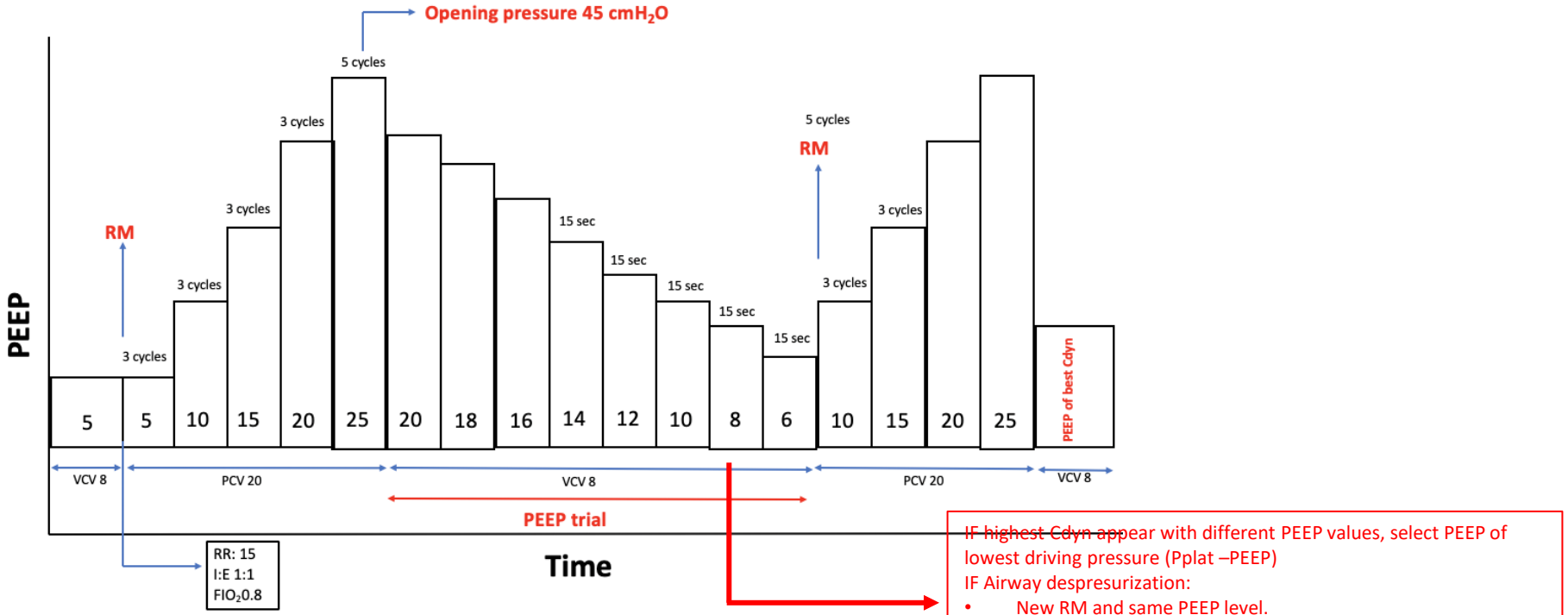
RECRUITMENT MANEUVER B + PEEP SETTING B

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.



When should RM and PEEP setting B be perfomed?

1. Rescue maneuver

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:*

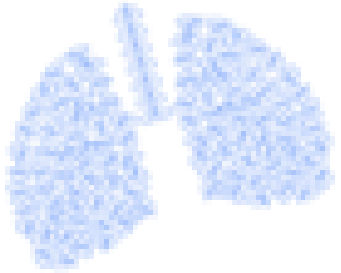
1. Collaborative capacity with CGS> 13.

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

3. VAS <4.

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

Case Report Form



iPROVE-EAL

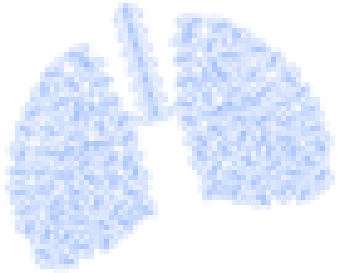
Individualized **P**eriope**R**ative **O**pen lung **V**E**n**tilatory approach in **E**mergency **A**bdominal **L**aparo-tomy/scopy. A prospective multicenter randomized controlled trial

Identifier	
HOSPITAL	
PATIENT IDENTIFICATION	
RESEARCHER 1	
RESEARCHER 2	

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

iPROVE Network Research Group
www.iprove.-network.es

Case Report Form



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

Postoperative Outcomes will be reported on days 1-3-5-7.

Yes is Yes, No is NO

Nothing is missing data. AVOID missing data!!!!!!

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	
☐ De novo Arrythmia	☐ Delirium	

Severe Adverse Events (SAEs)

- 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.
- The possible adverse events related to RMs that may appear are exceptionally electrical cardiac alteration that associates hemodynamic instability, and pneumothorax.
- Severe adverse events shall be documented in the specific CRF.

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:		