CLINICAL TRIAL PROTOCOL

Goal Directed Therapy Versus Standard Care in Lung Resection Surgery, a Randomized, Controlled Trial.

GDT-thorax Study

VERSION: v. 1.0 March 29th, 2017.

PRINCIPAL INVESTIGATOR

Alejandro Domínguez-Blanco, MD

Department of Anesthesiology. University Hospital Virgen del Rocío.

COLLABORATOR INVESTIGATORS

Manuel Bertomeu-Cornejo, MD-PhD

Ana Isabel Álvarez-Ríos, MD-PhD

Manuel de la Matta-Martín, MD-PhD

Juan Luis López-Romero, MD

Clara María Rosso-Fernández, MD-PhD

Isabel María Argueta-Hermoso, nurse collaborator

PLACE OF REALIZATION

University Hospital Virgen del Rocío

Avenida Manuel Siurot s/n

CP. 41013-Seville, Spain

SUMMARY

1.1. Type of request

This is a non-pharmacological clinical trial in which we are going to compare two types of hemodynamic management during lung resection surgery.

1.2. Sponsor

Fundación Pública Andaluza para la gestión de la Investigación en Sevilla (FISEVI). NIF: G – 41918830. University Hospital Virgen del Rocío. Ave. Manuel Siurot, s/n. 41013- Seville

1.3. Title

Goal Directed Therapy Versus Standard Care in Lung Resection Surgery (GDT-thorax Study).

1.4. Protocol Code

GDT-thorax. NCT03245372

1.5. Principal Investigator

Alejandro Domínguez Blanco, MD. E-mail: aledguez@gmail.com. Telephone number: 0034 660762856. Department of Anesthesiology. University Hospital Virgen del Rocío

1.6. Place of realization

University Hospital Virgen del Rocío, Seville. General Hospital.

1.7. Research Ethics Committee

Clinical Research Andalusian Central Ethics Review Committee

1.8. Responsible for Monitoring

Monitor: Reyes Fresneda Gutiérrez.

Coordination: Dr. Clara M. Rosso Fernández. Clinical Trial Unit (CTU). University Hospital Virgen del Rocío. General Hospital. Ground floor. Ave. Manuel Siurot, s/n. 41013- Seville.

2. GENERAL INFORMATION

A. Trial identificacion

A.1 Protocol code. GDT-thorax. NCT03245372.
A.2 Title. Goal Directed Therapy Versus Standard Care in Lung Resection Surgery.

B. Tipo de Ensayo Clínico

Non-pharmacological pilot clinical trial with sanitary product.

C. Sponsor

Fundación Pública Andaluza para la gestión de la Investigación en Sevilla (FISEVI). NIF: G – 41918830.
University Hospital Virgen del Rocío. Ave. Manuel Siurot, s/n. 41013- Seville, Spain.

D. Place of realization

The selection, treatment and follow up of the patients will take place in General University Hospital Virgen del Rocío: Post-anesthesia care unit, Thoracic surgery operating room (number 54) and Thoracic unit.

3. RATIONALE

Respiratory insufficiency is the main cause of mortality after thoracic surgery. The administration of high amount of fluids can worsen the respiratory complications. As consequence, fluid regimens in this surgery are restrictive. Nowadays, recommendations of fluid therapy in thoracic surgical procedures are summed up in the article of Chau et al in 2014:

- Total positive fluid balance in the first 24 hours postoperatively should not exceed 20 mL/kg.
- Crystalloid administration should be limited to <2 L intraoperatively and < 3 L in the first 24 hours postoperatively.
- Colloids should only be used to replace an equivalent volume of blood loss if blood is not required (maintain Hb > 80g). Maximum colloid volume = 1 L or an adult
- Urine output > 0.5 mL/kg/h is unnecessary in the early postoperative period unless the patient is at high risk of developing acute kidney injury.
- If increased tissue perfusion is needed postoperatively, appropriate invasive hemodynamic monitoring should be initiated to guide treatment with vasopressors, inotropes or fluid administration (1).

Nevertheless, a restrictive fluid therapy can lead to a situation of hypovolemia, with its corresponding risk of developing acute kidney injury due to low tissue perfusion. To administrate the proper amount of fluids, the concept of goal directed therapy (GDT) has gained widespread, helping us to discriminate what a patient needs in every moment (vasopressors, fluids or both).

There are clear evidences of the superiority of GDT over liberal fluid therapy in high risk patients (2,3), but this evidence is less clear if you compare GDT with normovolemic protocols aiming to get zero fluid balance, specially in patients enrolled in an enhanced recovery after surgery program (ERAS) (4). In cardiac surgery, 2 meta-analysis demonstrated a reduction in postoperative complications, ICU stay and hospitalary stay, but there was not a significant reduction in mortality (5,6).

In lung surgery, there are only two published articles of GDT, Zhang et al (7) in 2013 and Haas et al (8) in 2012. These articles use in their algorithms the systolic volume variation (SVV), a parameter which requires mechanically controlled ventilation (8 mL/kg ideal weight) and sinus rhythm. In this surgery, one lung ventilation, the opening of the thorax and the use of low tidal volume (4-6 mL/kg) makes SVV an unuseful parameter to guide hemodynamic management.

This study is designed to quantify and compare the hemodynamic control of cardiac index in patients who receive either goal-directed therapy or conventional hemodynamic management in lung resection surgery. With the help of the ev1000 clinical platform, we will analyze the percentage of the intraoperative time in which the cardiac index is equal or superior to 2.2 l/min/m2 (%). At the date of the elaboration of the study, this aspect has never been evaluated before, so we are going to conduct a pilot clinical trial.

References:

1.- Chau EH, Slinger P. Perioperative fluid management for pulmonary resection surgery and esophagectomy. Sem Cardiothorac Vasc Anesth 2014; 18:36-44.

2.- Hamilton MA, Cecconi M, Rhodes A. A systematicreview and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg 2011;112(6):1392-402

3.- Gurtel ST, do Nascimento P Jr. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. AnesthAnalg 2011;112(6):1384-91.

4.- Srinivasa S, Taylor MH, Singh PP, et al. Randomized clinical trial of goal-directed fluid therapy within an enhanced recovery protocol for elective colectomy. Br J Surg 2013;100(1):66-74.

5.- Aya HD, Cecconi M, Hamilton M, et al. Goal-directed therapy in cardiac surgery: a systematic review and meta-analysis. Br J Anaesth 2013;110(4):510-7.

6.- Giglio M, Dalfino L, Puntillo F, et al. Haemodynamic goal-directed therapy in cardiac and vascular surgery. A systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2012;15(5):878-87.

7.- Zhang J, Chen C, Lei X, et al. Goal-directed fluid optimization based on stroke volume variation and cardiac index during one-lung ventilation in patients undergoing thoracoscopy lobectomy operations: a pilot study. Clinics 2013;68(7):1065-1070.

8.- Haas S, Eichhorn V, Hasbach T, et al. Goal-directed fluid therapy using stroke volume variation does not result in pulmonary fluid overload in thoracic surgery requiring one lung ventilation. Crit Care Res Pract. 2012; 2012:687018.

9.- Piccioni F, Bernasconi F, Tramontano GT, et al. A systematic review of pulse pressure variation and stroke volume variation to predict fluid responsiveness during cardiac and thoracic surgery. J Clin Monit Comput. 2016 Jun 15. DOI 10.1007/s10877-016-9898-5

4. HYPOTHESIS AND OBJECTIVES

HYPOTHESIS

The investigators hypothesize that the percentage of the intraoperative time in which the cardiac index is equal or superior to 2.2 l/min/m2 is higher in goal directed therapy.

PRIMARY OBJECTIVES

The primary aim of this study is to quantify and compare the percentage of the intraoperative time in which the cardiac index is equal or superior to 2.2 l/min/m2 in patients who receive either goal-directed therapy or standard hemodynamic management in lung resection surgery.

SECONDARY OBJECTIVES

- To compare lactate, SvcO2 (central venous oxygen saturation) and PaO2/FiO2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) in the first 24 hours in both groups
- To compare fluid balance (differences between the amount of water taken into the body and the amount excreted or lost) in the first 24 hours in both groups
- To compare the incidence of AKI in both groups
- To compare the incidence of ARDS in both groups
- To compare hospital stay in both groups
- To compare the mortality rate in both groups

5. CLINICAL TRIAL DESIGN

5.1. Outcome measures

Primary outcome measures:

- Percentage of the intraoperative time in which the cardiac index is equal or superior to 2.2 l/min/m2 (%) [Time Frame: During the total duration of the surgery].

Secondary outcome measures:

- Oxygenation and tissue perfusion markers [Time Frame: Within 24 hours after lung surgery]

- Fluid balance [Time Frame: After 24 hours of finalization of lung surgery]

1) Inputs:
+ Fluid therapy (intra and postoperative, ml):
+ Insensible fluid input (due to oxidation): 300 ml/24 hours (12.5 ml/h).
+ Oral intake (water, ml):
2) Outputs:
+ Intraoperative bleeding (ml)
+ Urine output 24 hours (ml)
+ Insensible fluid loss: 0.5 ml/kg/h (24h)
+ Intrathoracic drainage (ml)
+ Thoracotomy: 1ml/kg/h surgery (0.5 ml/kg/h in case of video-assisted thoracotomy)

- Observation of acute kidney injury (AKI) [Time Frame: After 72 hours of finalization of lung surgery]

The AKIN classification/staging system of acute kidney injury		
Stage	Serum creatinine	Urine Output (UO)
1	↑ SCr ≥26.5 µmol/L (≥0.3 mg/dL) or ↑SCr ≥150 a 200% (1.5 a 2×)	UO < 0.5 ml/kg/h during > 6 h
2	↑ SCr >200 a 300% (>2 a 3×)	UO < 0.5 ml/kg/h during > 12 h
3	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 µmol/L (≥4 mg/dL) ↑SCr ≥44.2 µmol/L (≥0.5 mg/dL)	UO < 0.3 ml/kg/h during > 24 h or anuria during 12 h
Stage 3 also includes patients requiring RRT independent of the stage (defined by SCr and/or UO) they are in at the moment they initiate RRT.		

- Observation of acute respiratory distress syndrome (ARDS) [Time Frame: Within 30 days after lung surgery]

The Berlin Definition of Acute Rspiratory Distress Syndrome.
a) Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptons.
b) Chest imaging: Bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules.
c) Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need

objective assessment (eg. Echocardiography) to exclude hydrostatic edema if no risk factor present.	
d) Oxigenation:	
Mild	200 mm Hg < PaO_2/FIO_2≤300 mm Hg with PEEP or CPAP ≥5 cm H_2O *
Moderate	100 mm Hg < PaO_2/FIO_2≤200 mm Hg with PEEP ≥5 cm H_2O
Severa	100 mm Hg ≤ PaO_2/FIO_2 with PEEP≥5 cm H_2O
* CPAP may be delivered noninvasively in the mild acute respiratory distress syndrome group.	

- Duration of hospital stay [Time Frame: Within 30 days after lung surgery]
- Mortality [Time Frame: Within 30 days after lung surgery]

5.2. Randomization

The sampling method will be non-probability consecutive sampling. Randomization was conducted using random numbers obtained from statistical analysis tool EPIDAT (Epidat: Version 4.2, july 2016. Consellería de Sanidade, Xunta de Galicia, España; Organización Panamericana de la Salud (OPS-OMS); Universidad CES, Colombia. Available at: http://www.sergas.es/Saude-publica/EPIDAT). Patients will be recruited the day before the surgery, they will be informed about the trial and informed consent will be obtained. To prevent bias, randomization list will be guarded by the clinical trial unit. The anesthesiologist will call the clinical trial unit to obtain the randomization sequence when a patient is selected and the arterial line is placed.

5.3. Description of the trial treatments

Two groups:

- Arm A: Conventional hemodynamic management
- Arm B: Goal-directed therapy

Anesthetic protocol

1. Basic Anesthetic Monitoring: EKG, BP, SpO2.
2. Placement of peripheral venous line on the opposite arm of the surgery. 16 gauge if possible.
3. Administration of midazolam 2 mg IV if necessary.
4. Thoracic epidural catheter placement: T2-T6.
5. Biespectral index sensor placement.
6. Placement of **TOF-Watch** monitoring.

7. Induction:
    - Fentanyl 2 mcg/Kg IV.
    - Propofol 2 mg/Kg IV.
    - Rocuronium 0,6 mg/Kg, after calibration of TOF-Watch monitor.
8. Orotracheal intubation. Comprobation of correct placement of double lumen endotracheal tube with flexible bronchoscopy. Bladder catheterization.
9. Mechanical Ventilation, volume control. Tidal volume 8 ml/kg ideal weight, respiratory rate 12-14 breaths per minute. FiO_2 40% and positive end-expiratory pressure 5 cm H_2O.
10. Sevoflurane for maintenance of general anesthesia, BIS objective between 40 and 60.
11. **Antibiotic prophylaxis (**Cefazolin 2g IV). We repeat cefazolin 2 g three hours after the beginning of the surgery.
12. Placement of an arterial line on the radial artery of the opposite arm of the surgery. Invasive arterial blood pressure monitoring (FloTrac system). Obtaining baseline VSI and CI value. ARTERIAL BLOOD GAS SAMPLING (induction) AND LABORATORY BLOOD TEST (creatinine). ev1000 clinical platform (hemodynamic data collection).
13. **RANDOMIZATION (trial treatment),** Clinical Trial Unit, HUVR.
14. Central venous catheterization of the internal jugular or subclavian vein of the side of the surgery. VENOUS BLOOD GAS SAMPLING (induction).
15. Placement in lateral decubitus position. Inflation of the bronchial balloon of the double lumen tube after verification with fiberoptic bronchoscopy. Placement of thermal blanket.
16. Alveolar recruitment maneuver in bipulmonary ventilation: With pressure controlled ventilation, we set the inspiratory time at 50%, and we establish the respiratory rate at 12 rpm. The pressure over PEEP (Positive End-Expiratory Pressure) is kept constant at 20 cm H2O. The inspiratory pressure and the PEEP increase simultaneously and progressively from 30/10 to 35/15 and finally to 40/20 cmH2O. This last 40/20 cmH2O recruitment pressure is maintained for 10 cycles. Subsequently, the PEEP decreases gradually, returning to the baseline parameters, maintaining the PEEP at 7 cmH2O. After performing the recruitment maneuver, we return to volume controlled ventilation.
17. Begin unipulmonar ventilation. VT 4-6 ml / kg ideal weight. Start FiO2 at 80%, and progressively reduce to 50%, once stable SpO2 above 90% is achieved. PEEP 7 cm H2O. Respiratory rate that avoids auto-PEEP and aiming at PaCO2 values between 40 and 60 mm Hg (permissive hypercapnia). Airway peak pressures below 30 cm H2O. Alveolar recruitment in unipulmonar ventilation if necessary.
18. Epidural bolus of 5-7 ml of bupivacaine 0.1% plus fentanyl 5 mcg/ml.

19. **START OF SURGERY.**
20. ARTERIAL AND VENOUS BLOOD GAS SAMPLING (OLV-20 min). ev1000 clinical platform (hemodynamic data collection)
21. **Anesthetic Maintenance**:

    - Sevoflurane, bispectral index between 40-60.
    - Remifentanil, 0.03-0.05 mcg/kg/min.
    - Fluid and hemodynamic therapy according to allocation group.
    - **Rocuronium 5 mcg/Kg/min until 30 minutes before the estimated time to the end of the surgery.** TOF control every 45 minutes, seeking to maintain TOF < 3 signs.
    - Epidural continuous perfusion: bupivacaine 0.1% plus fentanyl 1 mcg/ml 5-7 ml/h. Begin 60 minutes after the initial bolus.
22. **30 minutes before the estimated time to the end of the surgery**:

    - Stop continuous perfusión of rocuronium.
    - Paracetamol 1 g (acetaminophen) or dipyrone 2 g IV.
    - Antiemetics: Ondansetron 4 mg IV (assess the risk of PONV, in case of high risk add 4 mg of Dexamethasone IV in the induction).
23. ARTERIAL AND VENOUS BLOOD GAS SAMPLING (End of surgery). ev1000 clinical platform (hemodynamic data collection)
24. **Emergence:**

    - Reversion of neuromuscular block:
        + If TOF < 3 signs, administer sugammadex 4 mg/Kg IV.
        + If TOF $\geq$ 3 signs or T_4/T_1 ratio < 0.9, administer sugammadex 2 mg/Kg IV.
    - **Extubation** when T_4/T_1 ratio > 0.9 and satisfactory spontaneous ventilation.

Arm A: Conventional hemodynamic management

On the basis of a continuous infusion of 2 ml/kg/h of balanced crystalloid solution (restrictive fluid therapy), the clinician will try to get basic intraoperative hemodynamic objectives: Heart rate 60-100 beats per minute, mean arterial pressure 65 mm Hg, serum lactate 2 mmol / L, oxygen saturation 95% (90% during one lung ventilation). The use of fluids and vasoactive agents will be at the discretion of the operating room anesthesiologist. The total of fluids administered in the intraoperative period will be fixed in a maximum of 2000 ml of crystalloid solutions.

Arm B: Goal directed therapy

The hemodynamic algorithm will be based on systolic volume index and fluid challenges. FloTrac sensor (this sensor connects to any existing arterial catheter and provides advanced hemodynamic parameters through pulse contour analysis) and EV1000 clinical platform (clinical platform from Edwards Lifesciences that provides advanced hemodynamic monitoring) will be used to calculate cardiac index and systolic volume index. The goal directed therapy target value is a cardiac index equal or superior to 2.2 l/min/m2.

3 steps:

-Step 1: ¿Cardiac index ≥ 2.5 l/min/m^2?

↓ No → ¿Systolic Volume Index (SVI) ≥ 35 ml/min/m^2)?

↓ No → Fluid Challenge* (250 ml plasmalyte in 10 min) → ⇧ 10% SVI

Yes → Bolus 250 ml** (Step 3)

No → Inotropes (Step 3)

↓ Yes → Inotropes (Step 3)

** Bolus is administered until IC ≥ 2.5 l / min / m2 or SVI increase is < 10%.

- Step 2: ¿Mean Arterial Pressure (MAP) ≥ 65 mm Hg?

↓ No → Vasoconstrictors for MAP ≥ 65 mm Hg (ephedrine, noradrenaline)

↓ Yes → OK

- Step 3: Reevaluate steps 1 and 2 every 10 minutes. In all cases, supplementary fluids will be administered to replace blood loss. RBC concentrates will be transfused to maintain hemoglobin above 8 g/dl. If coagulopathy is suspected, it will be corrected according to rotational thromboelastometry.

5.4. Procedures of the study and treatment duration

Patients undergoing thoracic surgery will have a preanesthesia evaluation. Once the surgical programming of the week is published, the inclusion criteria and the absence of exclusion criteria will be checked. We are going to compare two interventions: the use of goal-directed therapy versus conventional hemodynamic management.

The anesthetic technique will be the same in both groups, as well as the invasive techniques used (epidural, double lumen tube placement, arterial route, central line). The intervention finishes when the patient is extubated in the operating room, so both groups of patients will receive the same treatment in the postoperative period.

The patient will undergo daily clinical follow-up during the admission to monitor the appearance of complications, as well as to check the survival at first month. The detailed schedule of procedures is included in section 7.

5.5. Masking

The patient, investigators, surgeons and physicians responsible for postoperative care will be unaware of the treatment assigned. The anesthesiologist responsible for the patient in the intraoperative period will know the assigned intervention. All patients will be monitored as is protocolized in this type of surgery: invasive arterial pressure through a radial arterial catheter and central venous pressure through a central venous line in the subclavian or jugular vein. Through the FloTrac sensor, the information from the artery wave is transmitted to the EV1000 monitor, allowing us to have real time information about advanced hemodynamic values such as the cardiac index or the systolic volume index. Another investigator (not the operating room anesthesiologist) will collect the intra and postoperative data.

In the conventional hemodynamic management group, the anesthesiologist will not have access to the advanced hemodynamic data of the EV1000 monitor, but will have access to conventional monitoring data and analytical data, which are part of our routine management. For this reason, the ev1000 monitor will be covered with an opaque material.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Inclusion criteria

- Adults patients (18 years old)
- Written informed consent
- Elective lung resection surgery (open or thoracoscopic lung lobectomy)

6.2. Exclusion criteria

- Severe obesity
- Moderate to severe aortic insufficiency
- Renal failure requiring hemodialysis
- Left ventricle ejection fraction less than 35 %
- Urgent surgery
- Patient in critical care unit or a patient who will be transferred postoperatively to the critical care unit.
- Participation in another study that could interfere in the three months prior to the start of this study.

6.3. Criteria for withdrawal of patients

The patient can withdraw his consent to be included in the study at any time without explaining the reasons. The patient should withdraw from the study when:

- The subject requests to withdraw from the study or withdraw informed consent.
- The investigator considers that withdrawal is the best option for the patient, particularly in case of an adverse or intolerable event.
- Situation of hemodynamic instability of cardiological cause or massive hemorrhage that forces to increase the level of monitoring.
- Need to transfer to intensive care unit (ICU).

Follow-up of patients withdrawn from the study: If a patient is removed prematurely from the trial, the main reason for the suspension will be provided and, as indicated by the PCB rules, the usual procedures for the treatment of the pathology will continue.

Premature termination of the study: Premature termination of the clinical trial may occur by a decision of the regulatory authorities, for a change in the opinion of the Ethics Committee, for safety and/or treatment problems or indications of inefficiency. The sponsor reserves the right to interrupt the study in any time for reasonable medical and/or administrative reasons.

7. VISITS AND ASSESSMENTS:

7.1. Scheduled of visits and assessments (APPENDIX III)

7.2. Assessments for visits:

- Preanesthesia visit:
  - Clinical evaluation
  - ASA (American Society of Anesthesiologists) classification
- Selection visit (Day -1):
  - Informed consent form,
  - Preoperative clinical data (demographic data, previous diseases/medication).
- Day of the surgery visit (Day 0).
  - Hemodynamic data (EV1000).
  - Arterial and venous gasometry. In anesthetic induction, after 20 minutes of the onset of one lung ventilation and at the end of the surgery.
  - Adverse events
- 4 hours after surgery - visit (Day 0):
  - Laboratory test (creatinine, PCR)
  - Arterial and venous gasometry, hemodynamic data (EV1000).
  - Adverse events
- 24 hours after surgery - visit (Day 1):
  - Laboratory test (creatinine, PCR)
  - Arterial and venous gasometry, hemodynamic data (EV1000).
  - Adverse events
- 48 hours after surgery - visit (Day 2):
  - Laboratory test (creatinine, PCR)
  - Adverse events

- 72 hours after surgery - visit (Day 3):
    - Laboratory test (creatinine, PCR)
    - Adverse events
- 1 month after surgery - visit:
    - Adverse events
    - Survival

8. EFFICACY ASSESSMENT:

8.1. Efficacy assessment:

This evaluation will be made to all randomized patients:

• Hemodynamic control of the cardiac index.

• Incidence of acute renal failure.

• Incidence of acute respiratory distress syndrome, pneumonia, need for invasive or non-invasive mechanical ventilation.

• Incidence of postoperative nausea and vomiting.

• Incidence of atrial fibrillation.

8.2. Laboratory tests

The laboratory tests will be carried out in the local laboratories of H. U. Virgen del Rocio to measure the parameters mentioned below, which can be done more frequently if necessary. The gasometries will also be performed in the operating room gasometers. The determinations will include, at least, the following biochemical parameters:

- Creatinine, PCR.
- Arterial gasometry: Hemoglobine, lactate, PaO2, Hb, pH.
- Venous gasometry: Central venous oxygen saturation.

9. SAFETY ASSESSMENT

9.1. Methods for the evaluation of safety

Safety will be assessed in all patients participating in the study, which is by intention to treat (ITT). All adverse events (AE) occurring since the informed consent is signed until the final visit will be collected.

9.2. Definitions

Adverse Event (AE): Is any incidence detrimental to health in a patient or subject of a clinical trial treated with a drug, even if it does not necessarily have a relationship with such treatment. An AE can therefore be any unfavourable sign and unintended (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medication in research, whether or not it is related to the investigational medicinal product.

Adverse reaction (AR): is considered to be any harmful and unintended reaction to a research drug, irrespective of the dose administered. Unlike an AA, in the case of an RA there is a suspicion of a causal relationship between the investigational drug and the AE.

Imputability Criteria: the promoter will classify AA, based on their causal relationship with the drug, according to the Algorithm of Karch and Lasagna (1977), as:

- Definite: There is a reasonable temporal sequence between the administration of drug and the appearance of AA. This event coincides with the AR described for the drug, improves with suppression or reappears after its readministration and cannot be explained by alternative causes.
- Probable: there is a reasonable temporal sequence between the administration of drug and the appearance of AA. This event coincides with the AR described for the drug, improves after discontinuation of treatment and cannot be explained by other alternatives.
- Possible: there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the AR described for the drug but can be explained by alternative causes.
- Conditional or improbable: there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event does not coincide with the RAs described for the drug and can be explained by alternative causes.
- Not Related: there is no reasonable time sequence between the administration of the drug and the appearance of AA. This event does not coincide with the AR described for the drug and can be explained by alternative causes.

For the purposes of expeditious notification, the categories: definitive, probable and possible of

the algorithm of Karch and Lasagna (1977) will be considered as related and the conditional or unlikely category of said algorithm will be considered as unrelated.

The determination of the possible relationship with the treatment of the study is a responsibility of the principal investigator of the research centre or of the person designated by the latter.

Seriousness. Is considered severe any AE or AR that at any dose:

- Cause the death of the patient
- Threatens the life of the patient
- Require hospitalization or prolongation of patient hospitalization
- Cause disability or permanent or major disability
- It results in a congenital anomaly or malformation

For the purposes of notification, suspicions of AA or AR that are considered to be medically important, but not meet the above criteria, including medical events that require intervention to prevent any of the consequences described above, will also be notified as serious. All suspicions of transmission of an infectious agent through a medicine will also be considered serious.

Do not confuse the concept of "serious", described previously, with "severe" that refers to the intensity of AA or AR (mild / moderate / severe).

Serious and Unexpected Adverse Reaction (SUSAR)

Any serious AR whose nature, intensity or consequences do not correspond with the reference information for the drug. In this study, baseline information for the drugs being studied will be the technical file. The unexpected nature of an AR is based on the fact that it has not been observed previously and will not be based on what could be anticipated based on the Pharmacological properties of the medicinal product.

9.3. Adverse events management

9.3.1. Adverse events/pregnancy recording

Crucial data related to the AE are to be included on a specific form provided for the study. In order to collect all the information related to possible AE in the study, each study team will be trained during the site initiation visit on the definitions and rules for communication of an AE. Any AE, whether it is connected to the study medication or not, has to be recorded in the CRF which contains a specific pharmacovigilance section. Serious adverse events must be completed with more detailed information including the event description (according to international guidelines in pharmacovigilance), date of onset

and resolution, severity, assessment of causality to study medication, action taken and other concomitant medication/procedures used for the treatment of the AE. Any AE occurring is monitored using initial and follow-up communication until resolution.

The severe adverse event (SAE) form is centralized in the CTU and its personnel is responsible for reception (by fax or e-mail communication), registration and resolution of queries with participating sites. The identification of any SUSAR is assessed by a safety medical monitor in order to evaluate if information is to be communicated to Regulatory Authorities, Ethics Committees and Investigators following Good Clinical Practice (GPC) rules. In such a case, communication through the EudraVigilance system is foreseen. The safety medical monitor is responsible for any updates in safety information on the investigational medicinal product (IMP).

AA will be collected since the patient signs Informed Consent (CI) up to 28 days after administration of the last dose of the drug in investigation and/or last visit. All AA/pregnancy should be documented in the clinical history of the patient and in the CRF. All AAs should be monitored until their resolution, or at least during the 30 days after discontinuation of study drugs (whatever occurs first), until the toxicity returns to a degree ≤ 1, or until the toxicity is considered irreversible. In the case of collecting a case of pregnancy information will be collected on:

1. Normal birth, spontaneous or therapeutic abortion (any anomaly congenital detected in the aborted fetus must be documented), dead, congenital anomaly.
2. Neonatal deaths occurring within 30 days of birth.
3. Death of an infant after 30 days if the investigator suspects that he is related to intrauterine exposure to study medication.
4. All infants born after fetal exposure should be followed during the first 12 months after delivery.

Lack of efficacy and overdose should be considered as AA and be collected as such in the CRF. Any exacerbation of a pre-existing disease occurring after initiation of treatment of the study is also considered as an AA.Any abnormal results in the laboratory tests that the investigator considers clinically significant and requiring a dose adjustment of the treatment, the transient or permanent interruption of such treatment, or any other type of intervention or diagnostic evaluation to assess the risk associated with patient, will be collected as AA, and should be investigated and monitored adequately.

9.3.2. Adverse effects due to non-investigational medicinal products

NIMPs are "non-investigational medicinal products (IMPs)" referred in Article 2(d) of Directive 2001/20/EC, which may be provided to patients participating in a clinical trial according to the protocol.

For example, some clinical trial protocols require the use of pharmaceutical specialties as concomitant treatments or rescue due to prophylactic, diagnostic or therapeutic reasons and/or for ensure that subjects receive adequate medical care. They may also be used, according to the protocol, to induce a physiological response. These pharmaceutical specialties are not considered research drugs (IMP) according to Directive 2001/20/EC and PCB standards and are classified as "noninvestigational medicinal products" (NIMP). Any AA that may result from the administration of a NIMP should be collected in the CRF. If an SAE is considered to be related only to the NIMP and not relevant to the safety of the study, the investigator is obliged to communicate it, by Yellow Card, to the Pharmacovigilance Centre.

Procedure for notification of SAE/pregnancies (appendix I)

In the event of an SAE or a pregnancy case is collected, a member of the investigating team will complete and sign the notification form and will send it, by fax, immediately and always within 24 hours after having knowledge of the event to: Fax: 0034 954232992.

The CTU staff will review the form received and, if necessary, will request additional information from the investigator. When additional information is obtained, or it is resolved or unlikely to change, a follow-up report must be completed and faxed to the CTU. If there is a suspicion of a SUSAR, the investigator must provide the follow-up information requested by the CTU. Any SAE occurring more than 30 days after the end of treatment (without a time limit) should be reported if the investigator considers AAG to be related to the study treatment (i.e, if it is a serious adverse reaction) or if it is medically important.

It is not necessary to notify the CTU of the following SAE:

- Hospitalization or death due to the progression of haematological disease.
- Hospitalization for the performance of scheduled tests.
- Hospitalization to administer the study drug or to provide palliative care, terminal care or to perform scheduled surgical interventions.
- Hospitalization or prolongation of hospitalization to perform a procedure required by the protocol.
- Hospitalization or prolongation of hospitalization as a part of the routine procedure of the centre (for example, removal of a stent after surgery)

They will be collected in the CRF and in the patient's medical history.

Expedited notification of SUSARS to Health Authorities: The CTU will be responsible for notifying all the SUSARS collected in the study to the AEMPS, to the CEICs and to the Health Authorities, following the procedure indicated in the current legislation.

9.3.3. Notification deadlines

The maximum period for notification of an individual SUSAR suspect case shall be 15 calendar days from the date on which the promoter has had knowledge of it. When SUSAR is suspected of causing death the patient, or endangered his life, the promoter will send the information within 7 calendar days from the date on which he/she become aware of it.

9.3.4. Expedited notification of any other relevant safety information

The CTU will also notify, in an expeditious manner, all information that could modify the benefit/risk balance of the investigational medicinal product, or determine changes in the administration schedule or in the performance of the trial.

9.3.5. Annual safety reports

Safety annual reports are issued with all the safety information in the study being reported to regulatory Authorities and Ethics Committees.

9.3.6. Notification to investigators

The CTU will communicate to the investigators any safety information that may affect the safety of the trial subjects as soon as possible. The SUSAR information will be sent annually, in an aggregated form, in a list along with a brief analysis of the data provided. Throughout the study, the investigator will also be informed of any safety aspects that impact the conduct of the clinical trial or product development, including interruption of the development program or modifications to the protocol related to safety.

9.4. Discontinuation of study drugs due to adverse events.

Certain events or conditions may necessitate temporary or permanent discontinuation of study medication. Patients presenting such events or conditions will remain in the study and will be followed until completion. Any patient who interrupts the study medication should temporarily restart it as soon as possible.

Study procedures will be discontinued and will be replaced by out-of-study procedures with continuing the follow-up of patients. If the administered drug is permanently discontinued, subsequent therapy is left to the discretion of the investigator.

<u>Temporary discontinuation</u>

Criteria for temporary discontinuation of study drugs: The development of a toxicity that, depending on its nature and severity, requires a temporary discontinuation of study medication until the toxicity is resolved, as well as the development of another medical condition that would discourage the

administration of study drug. The decision to temporarily interrupt study medication in this situation will be left to the discretion of the investigator. The period during which patient is not taking the study medication will be as short as possible.

Permanent discontinuation

Criteria for permanent discontinuation of study drugs: Toxicity development requiring permanent discontinuation of any study drug, patient refusal to continue treatment, when in the opinion of the investigator continuing study therapy is not the best option for the patient and completion of the study.

10. STATISTICAL ANALYSES

10.1. Sample size:

With respect to the calculation of the sample size, we do not have data from previous studies or bibliography from any similar study that can be used to calculate the sample of our study, so we will carry out a pilot study (30 patients, 15 in each group). As it was mentioned before, the primary aim of this study is to quantify and compare the percentage of the intraoperative time in which the cardiac index is equal or superior to 2.2 l/min/m2 in patients who receive either goal-directed therapy or standard hemodynamic management in lung resection surgery.

10.2. Statistical methods

Normality of the data will be assessed using the Kolmogorov-Smirnov test. A descriptive analysis expressing qualitative variables as proportions and quantitative variables as mean (SD) or median and interquartile range (RIC), depending on if they follow a normal distribution or not, will be performed. In order to compare study groups, the Chi squared test or Fisher's exact test for qualitative variables and t Student's test or Mann-Whitney U, when necessary, in quantitative variables will be used. Analysis will be performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago III, U.S.A.) v 19.0.

10.3. Study limitations

The clinician performing the procedure cannot be blinded to the assignment of the treatment arm. The intervention is limited to the intraoperative period since the patients are extubated in the operating room. The follow up of postoperative morbidity and mortality is limited to one month. The study is not designed to have sufficient power to detect significant differences in major postoperative complications.

10.4. Efficacy analysis:

Efficacy analysis will be performed in two different populations: Intention-to-treat (ITT) analysis and per-protocol analysis. In an ITT population, none of the patients are excluded and the patients will be analyzed according to the randomization scheme. In a per-protocol analysis, only patients who complete the entire clinical trial according to the protocol will be counted towards the final results.

10.5. Safety analysis:

The safety analysis will be performed by intention to treat (ITT) in all randomized patients.

11. ÉTHICAL CONSIDERATIONS

11.1. Introduction

GDT-Thorax will be carried out in accordance with the Declaration of Helsinki principles (appendix II) and the legal norm directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human
use. Moreover, all local applicable rules such as Spanish Royal Degree 223/2004 will be considered for development of the study.

The trial will start after obtaining approval from a Central Ethics Review Committee (Clinical Research Andalusian Central Ethics Review Committee, CCEIBA), conformity from the Directors of the Institutions, and the authorization of the local ethic committee. A formal contract agreement was signed between each institution and the sponsor of the study.

11.2. Informed consent

The subject of the trial will grant his/she consent after having understood, through a previous interview with the investigator, the objectives of the trial, risks and drawbacks, as well as the conditions under which it will be carried out, and after being informed of their right to withdraw from the trial in any time without causing any harm.

Each study candidate patient will be provided with the corresponding informed consent in which the purposes of the research will be explained in addition to the procedures to be used, the expected duration of the research and the expected benefits to the patient and others.

Finally, each patient will be informed of the intention of publishing the results of the study in a scientific publication. To include a patient in the trial, he/she must give his or her informed consent to all assumptions.

Consent will be documented through an information sheet for the subject and the consent form. When the subject of the trial is unable to giving consent:

- If the subject is an adult without the capacity to give informed consent, the investigator will obtain the consent of the legal representative, having been informed about the possible risks, discomforts and benefits of the trial. The consent shall reflect the alleged wish of the subject and may be withdrawn at any time without detriment to him. When the conditions of the subject allows it, he/she shall also give its consent to participate in the trial, after having received all the relevant information adapted to their level of understanding. In this case, the investigator shall take into account the wish of the person unable to withdraw from the trial.
- When the subject is not able to make decisions due to physical or psychic state and has no legal representative, consent will be provided by individuals linked to him for family or de facto reasons. The subject participating in a clinical trial, or their legal representative, may revoke their consent at any time, without further explanation and without detriment to him.

11.3. Quality of data

There will be an exhaustive control of the data quality. CRF will be reviewed by the person in charge of monitoring. Investigators will fulfill the CRF, not knowing the the assigned treatment. Patients data will be exported to a SPSS database.

11.4. Protection of data

The confidentiality of records which could identify subjects in the GDT-Thorax study will be protected in accordance with the EU Directive 2001/20/EC. All laws on the control and protection of personal information will be carefully followed. The identity of patients will not be disclosed in the CRF; names will be replaced by an alphanumeric code and any material related to the trial such as samples will be

identified in the same way so that any personal information can be revealed.

11.5. Monitoring and audit

The study will be monitored through local visits, telephone calls and periodic inspection of CRF with sufficient frequency to check the following:

- Rate of inclusion of patients, compliance with the rules of the protocol procedures, data integrity and accuracy, verification with original documents and occurrence of EA.
- Monitoring visits will be performed by the study monitor. It is understood that she/he may access the medical records of the patients after requesting the researcher, who will facilitate access to the documentation to authorized persons.

11.6. Non-compliance

Non-compliance with the protocol and/or regulatory requirements from an investigator or from the staff members of the promotor should lead to rapid intervention by the promotor, to ensure compliance. If the monitoring and / or audit identify a serious and / or persistent non-compliance on the part of an investigator, the promoter must remove the investigator of the study. When the investigator is withdrawn due to noncompliance, it must promptly notify to the regulatory authorities.

11.7. Premature discontinuation

If the trial ends prematurely or is suspended, the sponsor must inform authorities of the completion or suspension and of the reason for it as specified by the regulatory requirements.

12. Financing and insurance policy

Every economic aspect in this trial will be written in a contract between the promotor and "Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla".

12.1. Insurance policy

Interventional level in this trial is low, because both interventions are similar to usual clinical practice. We will proceed to request the exemption of the contracting of the insurance policy for the

coverage of the possible civil responsibility that derives from some adverse events demonstrated on the subjects of this study.

13. Amendments to the protocol.

To ensure the study conditions and the valid statistical analysis of the data, neither the researcher nor the sponsor could alter the conditions agreed and stipulated in this protocol. Any amendment to the protocol which may have an impact on the development of the study or potential benefit for the patient, or which may affect patient safety would require a formal amendment to the protocol, such as changes in study objectives, study design, patient population, sample size, study procedures or significant administrative aspects. The study coordinator team and the CTU will agree such an amendment. Then, the amendment will become an integral part of the study protocol. In case the amendments require the approval of the ethical committees and/or Authorities, it must be obtained.

14. WORK SHEDULE

14.1. PHASES:

Randomized, controlled, blinded clinical trial with collection, observation and analysis of data.

14.2. RESOURCES AVAILABLE FOR THE REALIZATION OF THE CLINICAL TRIAL:

The selection, intervention and follow-up of patients will be carried out in: Conventional hospitalization of thoracic surgery, surgery room No. 54 and Post-anesthetic Recovery Unit of the General Hospital Virgen del Rocío. We will have the usual team of surgeons and nurses. There will be an anesthesiologist who will anesthetize all cases to avoid interindividual variability.

For the supervision of the investigation methodology and statistical analysis, we will have the advice of Dr. Juan Manuel Praena Fernández, from to the Research Support Unit of the Virgen del Rocío University Hospital (HUVR), together with Dra. Clara Rosso Fernández, from the Clinical Trial Unit of the HUVR.

The staff of the Clinical Trial Unit of the HUVR, will make the request of the clinical trial to the Clinical

Research Andalusian Central Ethics Review Committee, to the CEI of the University Hospitals Virgen Macarena and Virgen del Rocío and will be in charge of the coordination of the project. The assigned personnel will be responsible for the maintenance of the file and the documentation of the trial. A monitoring plan will be made and it will be ensured that the collected data correspond to the source documents and that the procedures indicated in the approved protocol are followed. The staff of the clinical research and clinical trials unit of the HUVR will be responsible for expeditious notification of serious or unexpected adverse events.

APPENDIX I. SERIOUS ADVERSE EVENTS NOTIFICATION FORM.

Unión Europea Fondo Europeo de Desarrollo Regional "Una manera de hacer Europa" SCReN Spanish Clinical Research Network	SERIOUS ADVERSE EVENTS (SAEs) NOTIFICATIONS FORM	Protocol code: GDT-thorax.
	Case No.: _____ Notification No.: _____	NCT: NCT03245372

Subject Code: _____			REPORT TYPE: ☐ Initial ☐ Follow-up		
1. SITE INFORMATION					
Site No.:	Principal investigator:				
SAE notifying entity:			Tel:		
Fax:	Email:				
2. SUBJECT INFORMATION					
Sex ☐ Male ☐ Female	Age (At the start of the AE) _____ ☐ Years ☐ Months ☐ Days	Age group (Fill in only if the subject's age is unknown) ☐ Newborn ☐ Infant ☐ Child ☐ Teenager ☐ Adult ☐ Older person	Date of birth (dd-mmm-yyyy) __-___-____	Weight (kg)	Height (cm)
3. ADVERSE EVENT					
Serious adverse event (Specify the diagnosis or syndrome, if known. If unknown, include signs and symptoms.]:					
DESCRIPTION OF ADVERSE EVENT (Provide all the information about the circumstances, sequence, diagnosis and treatment of the AE)					
Start date (dd-mmm-yyyy) __-___-____			End date: (dd-mmm-yyyy): __-___-____		
Severity criteria: ☐ Death ☐ Life threatening ☐ Requires or prolongs hospitalisation ☐ Permanent or significant disability ☐ Birth defect or congenital anomaly ☐ Clinically relevant			Outcome (status at the time of notification): ☐ Recovered ☐ In recovery ☐ Not recovered ☐ Recovered with sequelae ☐ Fatal ☐ Unknown		
In case of death fill in the following information: Date of death: __-___-____ Cause: _____ Was an autopsy performed: ☐ Yes ☐ No ☐ Unknown Indicate the cause of death according to the autopsy: _____					

4. INVESTIGATION MEDICINAL PRODUCT/DEVICE (Indicate the treatment(s) assigned to the subject after randomization)
If more space is needed, use copies of this page and tick this box ☐

Medicinal product	Dosage and units	Frequency	Route	Start date (dd-mmm-yyyy)	End date (dd-mmm-yyyy) (If this continues, tick this box)	Causal relationship
					☐	☐ Related ☐ Not related
					☐	☐ Related ☐ Not related
					☐	☐ Related ☐ Not related

Action taken with the medicinal product in response to the AE	☐ Withdrawal of the medicinal product ☐ Temporary interruption of the medicinal product ☐ Unknown	☐ Dose reduction ☐ Dose escalation	☐ Without changes ☐ Does not apply	
Did the AE abate after the medicinal product was withdrawn or the dose was reduced?	☐ Yes	☐ No	☐ Not known	☐ Not applicable
Did the AE reappear when the medicinal product was reintroduced?	☐ Yes	☐ No	☐ Not known	☐ Not applicable

5. CONCURRENT MEDICINAL PRODUCT (Include those concomitant and background treatments that were taken in the two weeks prior to the date of the AE. Do not include the treatment administered to treat AE or that given after the start date of the AE)
If more space is needed, use copies of this page and tick this box ☐

Medicinal product	Daily dose (units)	Frequency	Route	Start date (dd-mmm-yyyy)	End date (dd-mmm-yyyy) (If this continues, tick this box)	Causal relationship	Indication
					☐	☐ Related ☐ Not related	
					☐	☐ Related ☐ Not related	
					☐	☐ Related ☐ Not related	

Action taken with the medicinal product in response to the AE	☐ Withdrawal of the medicinal product ☐ Temporary interruption of the medicinal product ☐ Unknown	☐ Dose reduction ☐ Dose escalation	☐ Without changes ☐ Does not apply	
Did the AE abate after the medicinal product was withdrawn or the dose was reduced?	☐ Yes	☐ No	☐ Not known	☐ Not applicable
Did the AE reappear when the medicinal product was reintroduced?	☐ Yes	☐ No	☐ Not known	☐ Not applicable

6. ALTERNATIVE CAUSE

Is there any chance that the AE is related to any other alternative cause, other than the medicinal product?
☐ Yes ☐ No If yes, specify (write further information in the section of the SAE description, if necessary):

_____

_____

7. RELEVANT MEDICAL HISTORY
If more space is needed, use copies of this page and tick this box ☐

Pathological history	Start date (dd-mmm-yyyy)	End date (dd-mmm-yyyy)	(If this continues, tick this box)
			☐
			☐
			☐
			☐

Further information of the Medical History details

8. LABORATORY DATA AND OTHER ADDITIONAL TESTS: (show only test results which are relevant to document the notified SAE)
If more space is needed, use copies of this page and tick this box ☐

TEST CONDUCTED	TEST DATE (dd-mmm-yyyy)	RESULT (Units)	Reference range	REMARKS

Additional information of the laboratory data and other tests:

Signature of the investigator reporting the notification	Date of notification
Signature of the Pharmacovigilance Manager	**Date the notification was received**

IMMEDIATELY SEND BY FAX TO THE PHARMACOVIGILANCE NODE OF THE UICEC OF "HOSPITAL UNIVERSITARIO VIRGEN DEL ROCÍO"

(FAX: 0034 954 23 29 92)

APPENDIX II. WMA Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential

conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations, the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations, the research may be done only after for

such research. In such situations, the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention, less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.
Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's

judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX III. Scheduled of visits and assessments

	Preanesthesia visit	Selection (Day -1)	**Clinical data (before surgery) (Day -1)**	Day of the surgery (Day 0)	First postoperative day (Day +1)	Second postoperative day (Day +2)	Third postoperative day (Day +3)	End of follow-up (día +30)
Clinical evaluation	**X**							
ASA classification	**X**							
Inclusion/exclusión criteria		**X**	**X**	**X**				
Informed consent form		**X**						
Demographic data			**X**					
Previous diseases/medication			**X**					
Randomisation				**X**				
Surgery data				**X**				
Anestehesia data				**X**				
Follow up in post anesthesia care unit				**X**	**X**			
Arterial gasometry (lactate, PaO_2, Hb, pH) *				**X**	**X**			
Venous gasometry ($SvcO_2$) *				**X**	**X**			
Hemodynamic data (EV1000): CI, SVI, CVP, MAP *				**X**	**X**			
Laboraroty test (creatinine, PCR)				**X**	**X**	**X**	**X**	
Adverse events				**X**	**X**	**X**	**X**	**X**
Survival				**X**	**X**	**X**	**X**	**X**

* In anesthetic induction, after 20 minutes of the onset of one lung ventilation, at the end of the surgery, at 4 hours and 24 hours (postoperative).