Universitat de Girona

FINAL DEGREE PROJECT

LESS INVASIVE SURFACTANT ADMINISTRATION VERSUS INtubate-SURfactant-Extubate IN EXTREMELY PRETERM INFANTS WITH RDS. A STEP FORWARD. MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL

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1. LIST OF ABBREVIATIONS

a/A 02	Arterial/Alveolar index of oxygen
BPD	Bronchopulmonary Dysplasia
CREC	Clinical Research Ethical Committee
DR	Delivery Room
FiO_2	Fraction of inspired oxygen
GA	Gestational Age
HUDJT	Hospital Universitari Doctor Josep Trueta
INSURE	Intubation Surfactant Extubation
IVH	IntraVentricular Hemorrhage
LISA	Less Invasive Surfactant Administration
MAP	Mean Airway Pressure
MV	Mechanical Ventilation
nCPAP	Nasal Continuous Positive Air Pressure
NEC	Necrotizing Enterocolitis
NICUs	Neonatal Intensive Care Units
PDA	Patent Ductus Arteriosus
PEEP	Positive end-expiratory pressure
PMA	PostMenstrual Age
PNA	PostNatal Age
PPV	Positive Pressure Ventilation
PTBs	Preterm Births
RDS	Respiratory Distress Syndrome

RFC	Residual Functional Capacity
UdG	University of Girona
VI	Ventilation Index

2. ABSTRACT

Background: Pulmonary Surfactant therapy is commonly used for the treatment of the respiratory distress syndrome. This therapy is usually given to preterm infants who are mechanically ventilated using an endotracheal tube; however, non-invasive ways of administration are in study and try to avoid mechanical ventilation by the application of surfactant to spontaneously breathing infants. A method of surfactant delivery using a gastric catheter trough the trachea during spontaneous breathing with nCPAP seems to be potentially effective, reducing the need of MV and the incidence of Bronchopulmonary Dysplasia, and requires more investigation.

***Objective*:** The main aim of this study is to evaluate whether LISA technique is related to a lower need of MV and to a lower rate of BPD in extremely preterm infants with Respiratory Distress Syndrome than in infants treated with INSURE.

***Design*:** This study has been designed as a multicenter, randomized, two group controlled clinical trial, in which the reference center will be *Hospital Universitari Doctor Josep Trueta,* during a period of time of two years and six months.

***Methods*:** Preterm infants with GA<32weeks and with surfactant requirements, who can be stabilized with nCPAP in the delivery room, will be randomized to receive pulmonary surfactant therapy either by LISA procedure or INSURE technique. In both groups patients receive a dose of 200mg of Poractant α and will be followed up during a period of three months.

***Keywords*:** LISA (less invasive surfactant administration), INSURE (intubation-surfactant-extubation), surfactant, preterm infants, RDS (respiratory distress syndrome), mechanical ventilation.

3. INTRODUCTION

❖ Prematurity

Preterm births are a challenge for Perinatal Medicine. These infants are at risk of a big amount of complications which may compromise their life and have consequences in a short and long term. Although major advances in Perinatal Medicine have been introduced, the incidence of preterm deliveries has increased significantly among the most industrialized countries in the last decades.(1,2)

This information is sobering, since preterm infants have higher rates of morbidity and mortality. However, there are new resources available to allow greater survival, even in increasingly immature infants.

Definitions

A preterm birth is defined as a birth occurring before 37 completed gestational weeks, counting from the first day of the last menstrual period. Although the word preterm is used indifferently, it has no valuation on the maturity of the infant.

"Very preterm newborns" comprise those newborns whose gestational age (GA) is lower than 32 weeks, while an "extremely preterm newborn" would be born before 28 gestational weeks.(1,2)

Weight is also considered a reference to classify preterm infants as "low birth weight", <2500gr, "very low birth weight", <1500gr, and "extremely low birth weight", <1000gr.(1,2)

Epidemiology

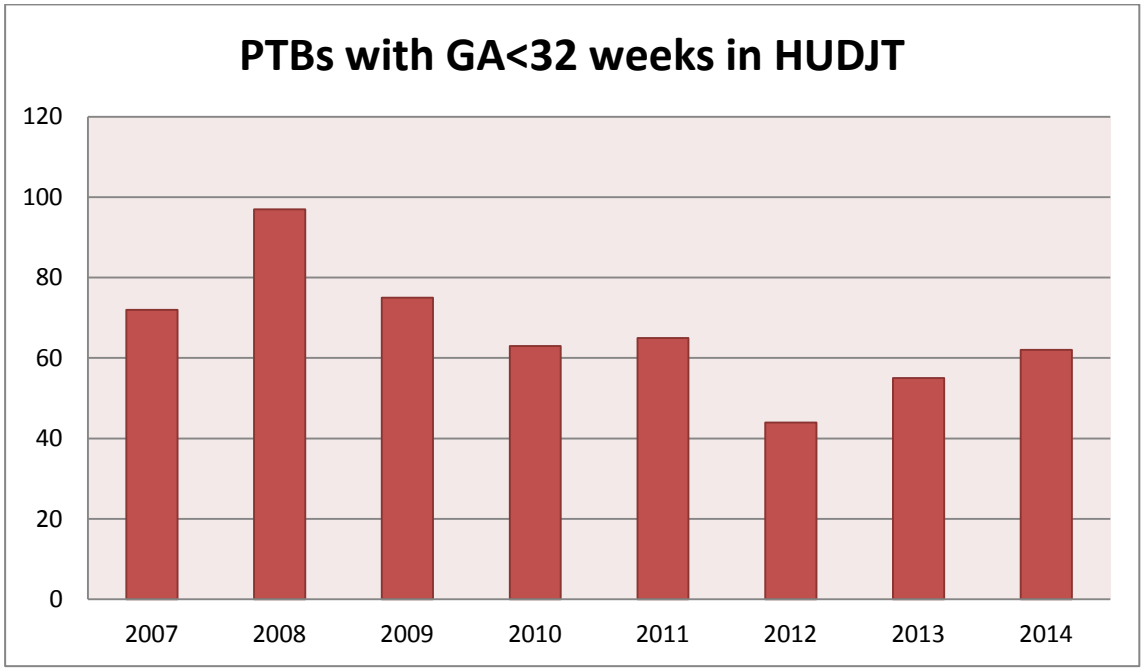
12.9 million preterm births were recorded in 2005, which represents a 9.6% of all births worldwide. Approximately an 85% of these newborns were concentrated in Africa and Asia. Just a 0.5 million PTBs were recorded in Europe and North America in each case.(3)

According to data available, the birth preterm rate in US has increased at least a 30% from 1980s.(4) In Spain, as the National Statistics Institute (INE) reports, the rate of prematurity between 1996 and 2012 varied from 5.27% to 5.58%.(5)

The *Agencia de Salut Publica de Catalunya* reports that in Catalonia, in 2013, a number of 4971 PTBs were documented out of a total of 70530 births, which is equivalent to a 7.1%. From the mentioned 7.1% of preterm births an 11% (546) corresponds to "very and extremely" PTBs (population included in the present study).(6)

Focusing on the data obtained from *Hospital Universitari Doctor Josep Trueta*, in 2014 there were 62 newborns with a GA<32 weeks, which is a significant increase over the previous year. In the figure below we can observe the variation of PTBs with GA<32 weeks in the last eight years.(7)

FIGURE 1: PRETERM BIRTHS DURING THE LAST EIGHT YEARS IN HUDJT



Causes and Risk Factors(2,8)

Preterm births, classified into spontaneous and indicated, are supposed to be initiated by multiple factors, including maternal conditions, pregnancy aspects and environmental and genetic interactions.

- **Spontaneous preterm births**

Most PTBs are initiated spontaneously and despite its difficulty to find out the precise cause, there is a variety of identified risk factors.

- Behavioral and Psychological contributors: excessive consumption of alcohol, smoking, cocaine use, unsuitable diet or psychosocial stressors such as emotional stress, living conditions, discrimination or even racism.
- Sociodemographic and community contributors: maternal age (<17 and >35 years increase the risk), race and ethnicity (black women have higher rates of PTB) and socioeconomic and

community conditions (through direct and indirect pathways, it is thought to be related to stress).

- Medical and pregnancy conditions: maternal medical illnesses and conditions (chronic hypertension, hypertensive disorders of pregnancy, lupus, hyperthyroidism, asthma, diabetes and cardiac disease), low weight gain during pregnancy, fetal conditions (placenta previa, uterine malformations, abruption of the placenta), previous PTBs and infections.

Multifetal gestations and the use of assisted reproductive technology are also risk factors. In fact, approximately 40% of twin gestations are delivered spontaneously before 37 weeks' gestation.

- **Indicated preterm births**

Maternal and fetal conditions can lead to indicated preterm deliveries: diabetes; preeclampsia or eclampsia; maternal cardiovascular and pulmonary disorders; placenta previa, abruption or uterine hemorrhagic events; fetal distress; multifetal gestations; polyhydramnios or oligohydramnios and congenital anomalies.

❖ Respiratory distress in the preterm infant

The Neonatal Respiratory Distress Syndrome (RDS), previously named Hyaline Membrane Disease (HMD)(9), is the most frequent acute respiratory disease of the preterm newborn.(9,10) It mainly, but not exclusively, affects patients with a GA<35 weeks and its incidence is inversely proportional to the gestational age, affecting the 80% of the PTBs<27 weeks.(11,12)

This pathology is a condition of pulmonary insufficiency that in its natural course commences at or shortly after birth and increases in severity over the first 2 days of life.(9,13) It is caused by a temporary surfactant deficiency, a tensioactive substance, produced by pneumocytes type II, which covers the alveoli; disabling adequate lung ventilation and gas exchange and leading to alveolar collapse.(9,12–14) Lung immaturity is also functional and morphological, since lung development is not completed in these immature infants.(2,15)

Clinically, RDS presents with early respiratory distress including cyanosis, grunting, retractions and tachypnea. It also presents hypoxemia and different grades of respiratory and metabolic acidosis associated to hypercapnia.(9,12–14) Blood gas analyses indicate possible respiratory failure development, and the diagnosis can be confirmed on chest X-ray with reveal a diffuse granular opacification of the lung parenchyma, in a classical 'ground glass' appearance, and air bronchograms.

In severe cases the radiological pattern may be “white lung”. If RDS left untreated death may occur from progressive hypoxia and respiratory failure.(4,9,12–14)

Clinical (4,9,12–14)

RDS clinical tend to appear immediately after birth or in the first hours of life, and include: polipnea and progressive signs of respiratory difficulty (whimper, produced by the air through the almost closed glottis, trying to maintain a right alveolar volume and to prevent collapse; toraco-abdominal dissociation; nasal flaring; use of the accessory muscles) with ambient air cyanosis.

This respiratory clinic is usually complemented with Patent Ductus Arteriosus with an initial left-right shunt that may complicate the RDS. Clinically it involves: tachycardia, hyperdynamic precordium, bounding pulse, and heart murmur and perfusion alterations.

Physiopathology (9,10,12,13,16)

In 1959 Avery and Mead demonstrated that in infants dying of RDS, surfactant deficiency had a key role in the pathogenesis of the disease.

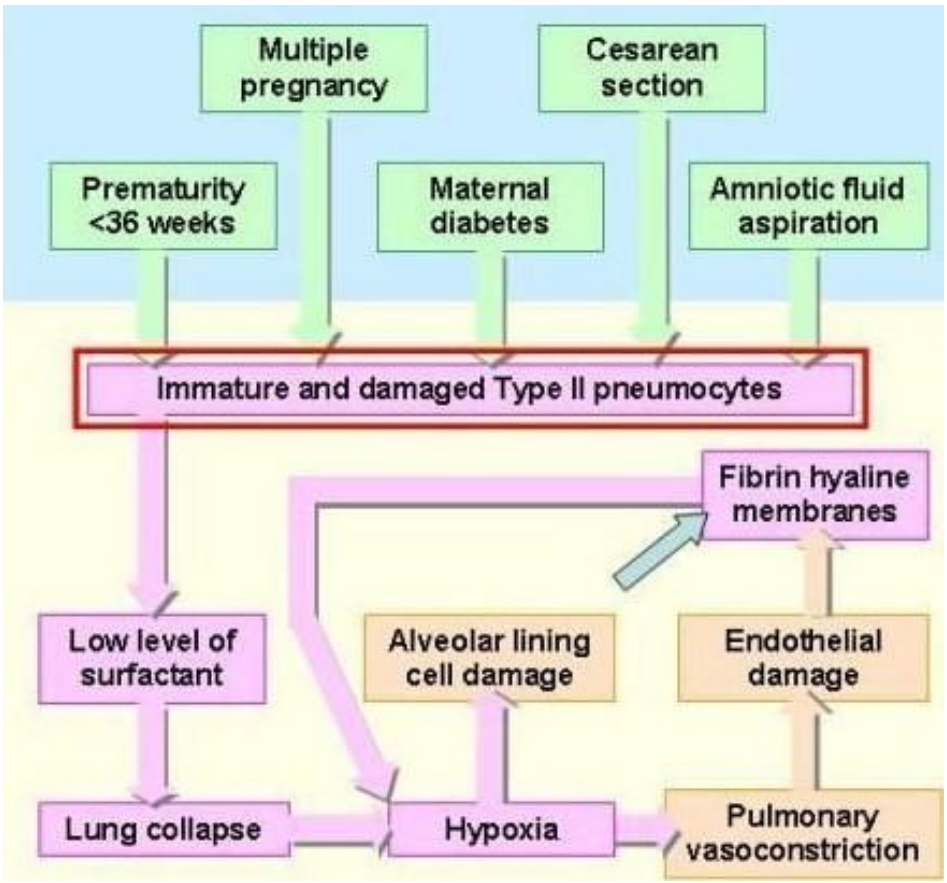
The decreased surfactant, caused by the alveolar collapse, reduces lung compliance and it subsequently results in a decrease of the functional residual capacity and an increase of atelectasis.

The following table resumes the histological changes lungs suffer and its respectively physiopathological effects.

FIGURE 2: HISTOLOGICAL CHANGES AND PHYSIOPATHOLOGY(13)

HISTOLOGICAL CHANGES	PHYSIOPATHOLOGY
• Areas of atelectasis and over-distension • Formation of hyaline membranes • Leaking of plasma proteins and fluid into air spaces • Alveolar epithelial cell necrosis	• Alveolar collapse and end-expiration • Reduced lung compliance • Decreased functional residual capacity • Increased dead space • Increased work of breathing

FIGURE 3: RDS PHYSIOPATHOLOGY(16)



RDS handling

The aim of management of RDS is to provide interventions that will maximize survival whilst minimizing potential adverse effects.(11)

- **Prevention:**(9,12,14,17,18)

It is very important to make an early detection and treatment of the premature delivery and the maternal prenatal corticosteroid treatment.

The corticosteroid pattern which is more indicated is with betamethasone i.m., two doses of 12mg separated at least 24-48h. Its effectiveness seems to be higher when the delivery occurs between 24h and 7 days after the treatment.(19,20)

Corticosteroids are indicated to those women with a threat of premature delivery with GA 24-34 weeks.(18–20)

- **Treatment:**(9,11–13,16,18)

Resuscitation in the delivering room**:** right stabilization in the birth scenario. In order to improve alveolar recruitment it is recommended to ventilate with PEEP in the delivering room, to start with early CPAP and to try to maintain it during the transfer to the NICU, preventing the alveolar collapse.

Support:

- Temperature: it is necessary to maintain a neutral thermal ambient; with this, oxygen requirements and deterioration of the metabolic acidosis will be reduced.
- Infections: a neonatal pneumonia or a sepsis would drastically deteriorate the prognosis; so that, in many cases of RDS form the birth, physicians start an empiric treatment with spread spectrum antibiotics until the bacterial cultures arrive.
- Monitoring: preterm infants with respiratory distress should be moved into a NICU as soon as possible. Heart frequency, breath frequency, arterial tension, oxygen saturation, gasometry and temperature have to be under control. Moreover, a chest radiography is necessary in order to make the right diagnosis.
- Nutrition and liquid administration: it is fundamental for the infant to have an adequate nutritional support but without an excessive overload of liquids, that would decline the respiratory situation.
- Hemoglobin: if the infant suffers an anemia the oxygen requirements will increase, therefore, it is important to maintain the best balance possible, valuing the transfusion when hemoglobin <11g/dl with oxygen support needs >30%.

Oxygen therapy: the main aim is to maintain a right oxygenation which allow a normal tissue function and prevent acidosis. These infants should preserve $Sat0_2$ 85-93%, according to that, physician administrate oxygen in adequate concentrations.

Surfactant therapy: Intratracheal surfactant administration has revolutionized neonatal respiratory care and it is the only specific treatment for the RDS.(11,12,21) It is necessary in those patients with moderate-severe RDS, with oxygen requirements and evidences of a need for early surfactant replacement; a $Fi0_2$ threshold 0.3 appears to give the optimal information to proceed to the exogenous pulmonary surfactant therapy.(12,22–24)

Surfactant

Pulmonary surfactant, a lipid-protein complex that modulates surface tension, plays a fundamental role in lung development and respiration.(13)

For a surfactant to function effectively two properties are essential: good compressibility to reach low surface tensions under pressure, on expiration, and rapid interface adsorption, on inspiration.

Composition:(9,13,16,18,25) surfactant is composed mainly of: phospholipids, neutral lipids and proteins.

Phospholipids make up over 80% of surfactant complexes. The most important phospholipids in mature surfactant are phosphatidylcholine (PC) and phosphatidylglycerol (PG). the major component of mature surfactant is called Dipalmitoylphosphatidylcholine (DPPC).

The neutral lipids are cholesterol and free fatty acids.

Four proteins associated to surfactant have been identified: *Surfactant Protein A*, its main role it thought to be host defense, it increases phagocytosis of bacteria; *Surfactant Protein D*, involved in the immune activity of the lung; and *Surfactant Protein B and C*, involved in spreading of surfactant phospholipids and adsorption of phospholipids.

Surfactant production and release:(13) surfactant is produced by type II cells within the alveoli. The distinguishing feature of these cells is the presence of lamella bodies, where granules for surfactant and secretion form the cells are storage by exocytosis of these bodies. The phospholipids are produced by intracellular mechanisms prior to packing into the lamellar bodies.

Preparations:(12,13) there are several different surfactant preparations that have been licensed for use in neonates with RDS including synthetic (protein-free) and natural (derived from animal lungs) products. The surfactants currently available in Europe are shown in Figure 4. Natural surfactants are superior to synthetic preparations, containing only phospholipids, at reducing pulmonary air leaks and mortality.

FIGURE 4: SURFACTANT PREPARATIONS LICENSED IN EUROPE IN 2013(12)

Generic name	Trade name	Source	Manufacturer	Dose (volume)
Beractant	Survanta®	bovine	Ross Laboratories (USA)	100 mg/kg/dose (4 ml/kg)
Bovactant	Alveofact®	bovine	Lyomark Pharma (Germany)	50 mg/kg/dose (1.2 ml/kg)
Poractant alfa	Curosurf®	porcine	Chiesi Farmaceutici (Italy)	100–200 mg/kg/dose (1.25–2.5 ml/kg)

Administration techniques:

INSURE technique: (24,26–28)this method of surfactant administration is considered the election according to actual guidelines. It consists on the administration of surfactant through a double lumen endotracheal tube, with previous sedation and with the support of MV. The aim of such method is to maintain the MV during de process (surfactant is introduced in the smaller lumen of the tube) and to extubate the patient in the following minutes (we will consider acceptable 30 minutes after surfactant administration later in this study).

LISA technique:(11,12,23,24,28–31) Under the denomination of less invasive surfactant administration (LISA) there are some techniques that aim to provide surfactant replacement without intubation and especially avoiding MV. Among the techniques involving brief tracheal catheterization, there are two fundamental methods, the Hobart and the Cologne method. There are others which are, in general, modifications of one of these techniques mentioned(24,29):

- *The Hobart method*

  The Hobart method uses a semi-rigid vascular catheter to instill surfactant under direct laryngoscopy. Interestingly, this method does not need Magill's forceps.

- *The Cologne method*

  This method uses a gastric catheter or similar, but requires the aid of the Magill's forceps to position the tip of the catheter through the vocal cords.

  Both methods are thought to show sustained improvement in oxygenation, with a reduction in duration of oxygen supplementation and need for early MV.

Spontaneous breathing during the process and the use of minimally sedative drugs, which depress the respiratory drive, seem to have a positive effect on the distribution of surfactant.(23,24,28)

In this study a modification of the Cologne method will be used in a group of patients compared to a group treated with INSURE method.

❖ **Justification**

Despite the medical advances, prematurity is still a big challenge to perinatal medicine. The RDS is the most important cause of mortality and morbidity in preterm infants although thanks to exogenous pulmonary surfactant therapy there have been substantially improvements(24). However, recent studies available(11,21,23,24,28–32) discuss the way of administration of this drug.

So far, the INSURE technique is thought to be the most efficient one to treat the RDS requiring tracheal intubation, surfactant administration and rapid extubation, although the latter is not always possible. Almost 10% of the infants solely intubated for surfactant administration cannot be extubated after the procedure. In addition, the intubation of the trachea is an invasive procedure and it also involve some risks.(23,24,28,31)

Late studies suggest less or minimally invasive surfactant administration techniques and the results show that it can reduce the MV need and also interfere in the incidence of BPD in this group of patients, who are more likely to develop it.(23,24,28,31)

Even though the results were promising there are little evidences and the information is not yet conclusive as further studies are expected to answer more outstanding questions, as well as further investigation is required to confirm optimal strategies and the population in which the effect would be the greatest.

Due to the mentioned before, we have designed this multicenter clinical trial which may provide:

- Results from a wider sample size: most clinical trials performed(21,23,29,30) use low samples, so that, we consider it is the first study that involves enough patients to extrapolate the results.
- After reviewing and considering some studies that involve children with GA>32 weeks, we have decided to avoid those infants, who could create errors in the results for their better recovery, in our study. We consider that from 24 weeks of gestation to 32 a big difference may already be observed in their evolution. Therefore, we do not consider involving those with GA>32 weeks to be appropriate either to minimizing the errors in our results or to clarifying the group of patients that would benefit the most the new technique.
- We have also tried to elaborate a careful methodology and quality control of the data recorded to have the most accurate results possible. Equivalent doses of surfactant will be administrated in the controlled groups in order to avoid the bias on the need of a second dose of surfactant that a Spanish trial(23) had in their results.

- Finally, we consider that the studies performed in our country are few and inadequate(23,29,30) to have an impact in the healthcare system, so we suggest the present multicenter study to be able to extrapolate the results to the population of our country and to have a great impact on the clinical practice.

4. HYPOTHESIS

- ❖ LISA techniques reduce the need of MV in preterm infants with respiratory distress syndrome compared to INSURE techniques.
- ❖ The incidence of BPD is significantly lower in patients treated with LISA techniques rather than those treated with INSURE techniques.

5. OBJECTIVES

- ❖ This study aims to determine the effectiveness of Less Invasive Surfactant Administration techniques on extremely preterm infants with Respiratory Distress Syndrome compared to INSURE therapy.

Primary objective

- ❖ To determine if extremely preterm infants with RDS who have been treated with LISA procedure need less MV at the 72h of life than the ones treated with INSURE technique.

Secondary objectives

- ❖ To certify if patients treated with LISA technique have a lower incidence of BPD than patients treated with INSURE.
- ❖ To determine if patients treated with LISA procedure have a lower incidence of PDA than patients treated with INSURE.
- ❖ To verify if patients treated with LISA have a lower rate of IVH than patients treated with INSURE.
- ❖ To demonstrate if patients treated with LISA procedure have a lower incidence of retinopathy than patients treated with INSURE.
- ❖ To learn if patients treated with LISA procedure have a lower incidence of NEC than patients treated with INSURE.

6. METHODOLOGY

❖ Study design

The present study has been designed as a multicenter, randomized, two group controlled clinical trial in order to evaluate the efficacy and safety of a less invasive technique for the administration of surfactant in preterm patients with respiratory distress syndrome, compared to the actual treatment: INSURE.

❖ Participants

The study population is based on "very preterm" and "extremely preterm" newborns with the following criteria:

Inclusion Criteria

- Newborns with GA <32 weeks diagnosed with Respiratory Distress Syndrome
- FiO_2>30%
- Either gender
- Paternal written informed consent

Exclusion Criteria

- Infants with major congenital anomalies
- Infants who required PPV or intubation in the DR

❖ Sample selection

A consecutive non-probabilistic sampling will be used. This is a multicenter trial, in which the HUDJT and three other centers will be involved. The sample recruitment will take place in the Neonatal Units from the centers affiliated to the study, during a period of time of approximately two years and three months.

The patients will be under medical attention and parents of those likely to meet inclusion criteria will be given an information sheet describing the study and inviting them to join (see ANNEX 1). Those interested in enrolling the study will be attended by a trial doctor who will review the study planning and obtain an informed consent (see ANNEX 2).

❖ Sample size

In order to calculate the sample size of our project Sample Size Calculator GRANMO was used.(33) Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 189 subjects will be necessary in each group, making a total of 378 patients, in order to find a statistically significant proportion difference. We estimate a difference of about 15%(23,24,28) on the need of MV between the two groups meant to be 0.45 in the INSURE group and 0.3 in the LISA group. A dropout rate of 5% has been anticipated.

In order to achieve a sample of 378 patients a multicenter clinical trial is suggested; four hospitals with NICUs level III from Catalonia, named below, will be asked to participate:

- **Girona**: *Hospital Universitari Doctor Josep Trueta*.
- **Barcelona**: *Hospital Maternoinfantil Sant Joan de Déu, Hospital Vall d'Hebron, Hospital Universitari Parc Taulí Sabadell*.

With the adequate collaboration and coordination, we can enroll 378 PTBs with all criteria needed in approximately 2 years and three months. Although it could be done in less time, we suggest a longer period of recruitment, inferring that it is an acute stressful situation and the participation rate will be lower.

❖ Intervention

Randomization

All newborns with GA<32 weeks admitted in the NICUs from the hospitals adhered to our clinical trial which meet all criteria needed to take place in the study and whose parents, after being well informed (Patient Information Sheet ANNEX 1), accept the Informed Parental Consents (ANNEX 2), will be eligible for the trial.

A statistical specialist will be responsible to elaborate a randomization sequence using statistical software. This will provide a probability sampling, a simple random sampling.

Thus, we will obtain a code for each patient that will be provided to the healthcare professional responsible of the care and treatment of the patient. This schedule will let them know in which group is every child allocated in order to realize the properly technique of surfactant administration.

The mentioned statistical specialist and the statistical that will be hired to analyze the data collected will not be the same person, thus data will be blinded to the responsible of the statistical analysis.

Procedure of INSURE and LISA

- **LISA GROUP (A):** intratracheal surfactant administration technique to preterm newborns in spontaneous breathing with non-invasive therapy support and with surfactant therapy criteria (FiO_2>0.3, taking into account his/her GA, respiratory pathology, hours of life, progressive increase of his/her oxygen needs…) using a catheter.

Preparation of the patient:

- Optimization of the patient's respiratory situation via aspiration of nasopharyngeal secretions, adjustment of PEEP in order to reach the maximum alveolar recruitment. It is usually necessary to increase FiO_2 10-20% previously and during the procedure.
- Administration of 20mg/kg of Caffeine Citrate to prevent apneas and bradycardia.
- Administration of 0.02mg/kg of Atropine to reduce oropharyngeal secretions and vagal reflex.
- Appreciate if analgesia is needed. Oral sucrose may be administrated to the patients who experience discomfort or resistance to the technique. Fentalino or Propofol will be used in selected patients according to physicians' judgment.

Material:

- Catheter to administrate the surfactant dose (4F nasogastric tube).
- Straight blade laryngoscope.
- Magyll forceps.
- Lubricant for the catheter if needed.
- Aspiration equipment for the oropharyngeal secretions.
- Neonatal ventilation equipment and material for a conventional intubation prepared just in case of a failure of the technique.
- Surfactant doses: 200mg/kg.

Technique:

- The patient must be disposed in supine decubitus.
- Right containment of the head and extremities procuring the maximum comfort of the patient and the best subjection of the ventilation system.
- Introduction of the laryngoscope following the usual intubation procedure.

- Introduction of the intratracheal catheter, Magyll forceps will be needed to help in the process. Initially, the tube can be introduced 8-9cm as it can be extracted accidentally removing the laryngoscope.
- Once the laryngoscope has been removed, check that the measure introduced from the oral commissural is 6cm + newborns' weight.
- Surfactant administration must be slowly in order to prevent regurgitation of the drug and to ensure the best distribution.
- Purge the tube with 1-2cc of air to introduce the remaining surfactant before removing it.
- Readjust the ventilatory and oxygen requirements according to the response.
- Remove the catheter.

The doctor in charge of the patients will ensure the security of the newborn anyway. If the child presents any questionable conduct the physician will precede to another therapy according to his/her experience and in the only benefit of the infant. The technique will be considered as a failure if the patient needs to be intubated during the procedure.

- **INSURE GROUP (B):** surfactant administration technique to preterm newborns with surfactant therapy criteria (FiO_2>0.3, taking into account his/her GA, respiratory pathology, hours of life, progressive increase of his/her oxygen needs…) using MV, an invasive therapy.

Preparation of the patient:

- Optimization of the patient's respiratory situation via aspiration of nasopharyngeal secretions, adjustment of PEEP in order to reach the maximum alveolar recruitment.
- Administration of 20mg/kg of Caffeine Citrate to prevent apneas and bradycardia.
- Administration of 0.02mg/kg of Atropine to reduce oropharyngeal secretions and vagal reflex.
- Analgesia with Fentanilo or Propofol according to the physician's judgment.

Material:

- Endotracheal tube double lumen.
- Straight blade laryngoscope.
- Magyll forceps.
- Lubricant for the endotracheal tube.
- Aspiration equipment for the oropharyngeal secretions.
- Neonatal ventilation equipment.

- Surfactant doses: 200mg/kg.

Technique:

- The patient must be disposed in supine decubitus.
- Introduction of the laryngoscope following the usual intubation procedure. Flashing PPV if it is required.
- Introduction of the endotracheal tube, Magyll forceps can be used to help in the process. Nasal or oral intubation will be realized according to the physician experience. In both cases the tube must be introduced initially 8-9cm as it can be extracted accidentally removing the laryngoscope.
- Connect to mechanical ventilation to preserve patient's breath.
- Once the laryngoscope has been removed, the measure introduced must be checked. For nasal intubation 7cm + weight of the patient, for oral intubation 6cm + weight of the patient.
- Surfactant administration through the smaller lumen of the tube. It must be slowly introduced in order to prevent regurgitation of the drug and to ensure the best distribution.
- Purge the tube with 1-2cc of air to introduce the remaining surfactant before removing it.
- Readjust the ventilatory and oxygen requirements according to the response.
- Extubation and collocation of a nasal CPAP in the following 30 minutes if it is possible. In the case that the patient needs to be intubated more than 30 minutes the technique will be considered to be a failure and that the patient needs invasive ventilatory support.

During the procedure patients will be monitored and if there is any alteration in the register the physician will proceed to preserve patients' security.

Follow up

All patients will be followed up during a period of three months. During this time physicians and nurses contributing to the study will take care of them and collect all data needed for the study.

In both groups, if the technique can be carried out with success, the following steps will be followed:

- Gasometry just after the technique and every 6 hours until a FiO_2<25% is registered.
- Daily complete blood tests the first 72h, then analysis will be done every two days until the 10^{th} day of life.

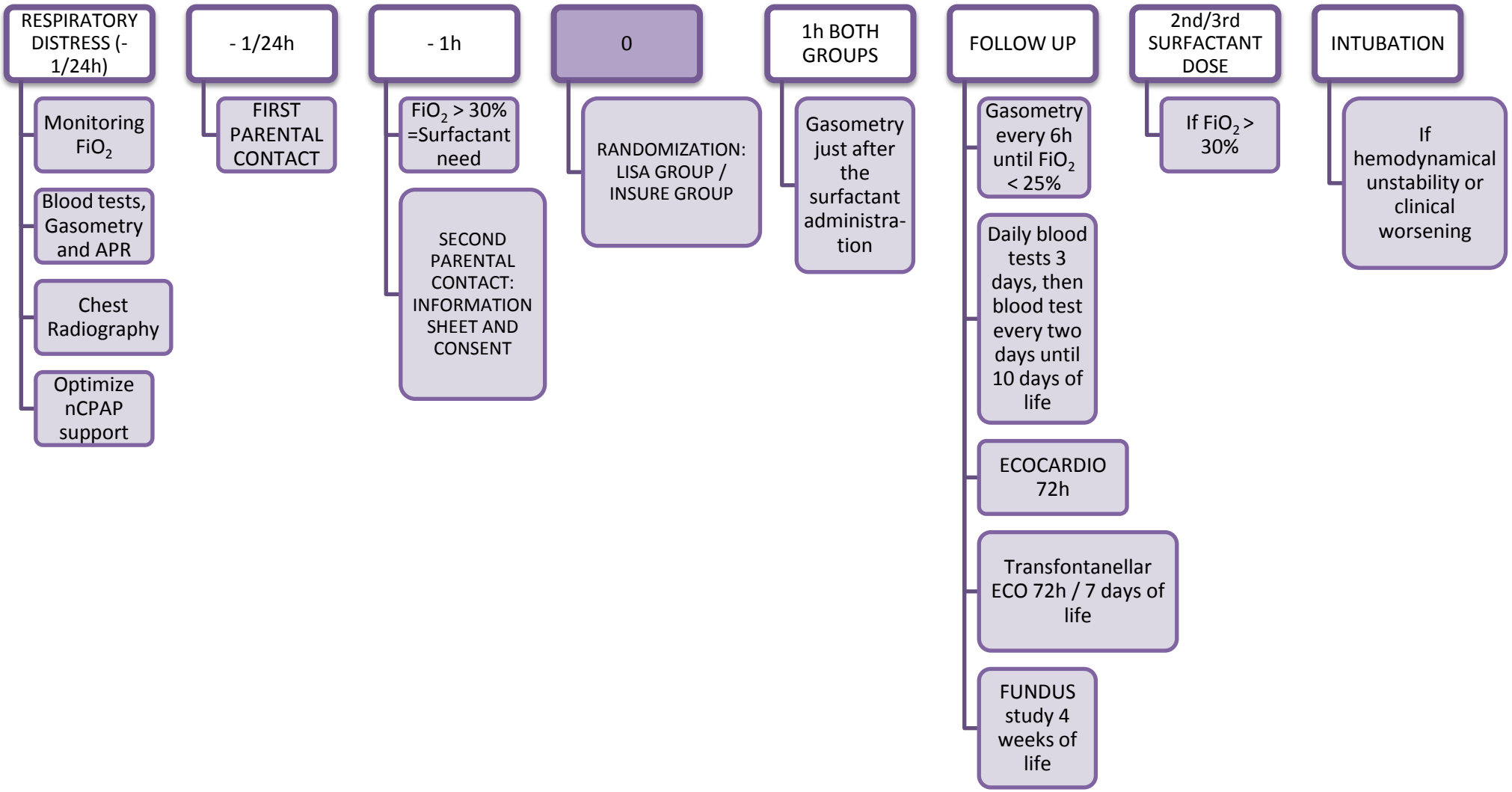
- Heart ecography at 72h of life.
- Transfontanellar ultrasound at 72h of life and at the 7th day of life. Then, weekly controls.
- Fundus study 4 weeks after birth, according to the findings periodic controls will be done.

If in any case the FiO_2 is over 30% the physician will have to consider the need of intubation or the need of a second dose of surfactant (if it is necessary we can administrate up to three doses. The second and the third doses of surfactant will be of 100md/dl). If the patient is hemodynamically unstable or if there is a clinical worsening (also observed in the chest radiography and gasometry) the doctor will proceed to intubate in order to guarantee the patient's security.

All tests realized to preterm infants involved in our study, and explained in the intervention section, are presented schematically below: Figure 5.

Patient intervention scheme

FIGURE 5: PATIENT INTERVENTION SCHEME



❖ **Variables and assessment**

Independent

- **LISA technique**: less invasive technique to administrate exogenous surfactant to those patients with requirements. In this study, a modification of *The Cologne method*(24,29) will be performed, using a nasogastric catheter. [See more details of the technique in the *Intervention*].

It will be measured as a nominal qualitative variable.

- **INSURE technique:** invasive surfactant therapy. [See more details of the technique in the *Intervention*].

It will be measured as a nominal qualitative variable.

Dependent

Primary dependent variable:

- **Mechanical Ventilation** at 72h of life.

Description: It will be measured as a dichotomous nominal qualitative variable (yes or no) and will be described as a proportion.

Secondary dependent variables:

- Days of **MV** need.

Description: If MV is required, we will register the number of days that the patient will be under the mentioned respiratory support. It will be measured as a quantitative variable and will be described as mean ± standard deviations.

- Days of **nCPAP** need.

Description: It will be measured as a quantitative variable and will be described as mean ± standard deviations.

- Need of **oxygen** (O_2) and duration.

Description: The need of oxygen therapy will be measured as a dichotomous nominal qualitative variable and described as a proportion; the duration of the mentioned therapy will be measured as a quantitative variable and described as mean ± standard deviations.

- Incidence of **BPD** and staging.

Description: Bronchopulmonary dysplasia is defined as the supplementary oxygen need >21% during a period of time of at least 28 days.(34) The severity determination may allow identifying the evolution and following up of the patient. According to general agreements, radiological findings, for its subjective interpretation, will not be considered for defining or evaluating the severity grade. Therefore, diagnostic criteria and severity classification are described in the following figure.(34)

FIGURE 6: BPD DIAGNOSTIC CRITERIA AND CLASSIFICATION

	Gestational Age	
	<32 weeks	*≥32 weeks*
Evaluation moment	36 weeks PMA	>28d but <56d PNA
Oxygen support	>21% during ≥28 days	>21% during ≥28 days
Bronchopulmonary Dysplasia:		
• Mild BPD	Ambient air breathing	Ambient air breathing
• Moderate BPD	FiO_2 <0.30	FiO_2 <0.30
• Severe BPD	FiO_2 ≥0.30 and/or nCPAP or MV	FiO_2 ≥0.30 and/or nCPAP or MV

PMA: PostMenstrual Age; PNA: PostNatal Age

The incidence of BPD in the preterm infants of our study will be measured as a dichotomous ordinal qualitative variable and described as a proportion.

- **Mortality**.

Description: Mortality will be measured as a dichotomous nominal qualitative variable and described as a proportion.

- Incidence of **IVH** and staging.

Description: Intraventricular hemorrhage is the most frequent cerebral lesion in the preterm newborn. Generally, it causes no symptoms and its diagnosis is done by a transfontanellar ultrasound. Clinical and neurological repercussions are observed in patients with massive bleeding.

IVH classification according to location and intensity of the bleeding is observed in the figure below.(35)

The incidence of IVH will be measured as a dichotomous ordinal qualitative variable and described as a proportion.

FIGURE 7: IVH CLASSIFICATION(36)

INTRAVENTRICULAR HEMORRHAGE	
MILD	GI: Isolated hemorrhage in the germinal matrix GII: IVH with normal ventricular size
MODERATE	GIII: IVH with acute ventricular dilatation
SEVERE	GIV: Intraventricular and parenchymal hemorrhage

- Incidence of **Patent Ductus Arteriosus** (PDA) and staging.

Description: The Ductus Arteriosus is a vascular structure which connects the Proximal Descending Aorta with the Principal Pulmonary Artery near the Left Pulmonary Artery origin. It is essential for fetal life and it closes spontaneously after birth, although in preterm infants it usually lasts a week to close, especially in those children who need MV. Therefore, the PDA is the failure of closure of the Ductus Arteriosus after birth. The diagnosis will be done by a heart ecography.(37) We will focus on the PDA that precise pharmacological or surgical treatment.

The incidence of PDA will be measured as a dichotomous ordinal qualitative variable and described as a proportion

- Incidence of **Necroting Enterocolitis** (NEC) and staging.

Description: Necroting Enterocolitis is a severe disease which affects newborn, especially preterm infants, and it is presented as a gastrointestinal and systemic syndrome, with hypersensibility and abdominal distension, blood in stool, food intolerance, apnea, lethargy and in advanced cases acidosis, sepsis and even shock.(38)

A part from the physical exploration, in order to confirm the diagnoses it is essential an abdominal radiography. The modified *Walsh and Kliegman Classification* shows the following findings according to each stage of the disease.(38)

The incidence of NEC will be measured as a dichotomous ordinal qualitative variable and described as a proportion.

FIGURE 8: WALSH AND KLIEGMAN NEC MODIFIED CLASSIFICATION(38)

WALSH AND KLIEGMAN NEC MODIFIED CLASSIFICATION			
STAGE	**SYSTEMIS SIGNS**	**DIGESTIVE SIGNS**	**RADIOLOGY**
I a: Suspected	Apnea, bradicardia, lethargy, temperature alteration	Residual, distention, vomiting	Negative
I b: Suspected	Apnea, bradicardia, lethargy, temperature alteration	Blood in stool	Negative
II a: Mild NEC	Apnea, bradicardia, lethargy, temperature alteration	Ileum, hypersensibility	Dilatation, ileum, pneumatosis
II b: Moderate NEC	Apnea, bradicardia, lethargy, temperature alteration, acidosis and trombopenia	Hypersensibility, mass	Dilatation, ileum, pneumatosis, portal gas, possible ascitis
III a: Severe NEC	Apnea, hypotension, bradicardia, acidosis, neutropenia, DIC	Peritonitis, distension, erythema	Dilatation, ileum, pneumatosis, portal gas, ascitis
III b: Severe NEC with perforation	Apnea, hypotension, bradicardia, acidosis, neutropenia, DIC	Peritonitis, distension, erythema	Dilatation, ileum, pneumatosis, portal gas, ascitis, pneumoperitoneum

- Incidence of **Retinopathy**.

Description: The Preterm Retinopathy is an ocular disease often seen in preterm infants. It is caused by an abnormal development of the retinal blood vessels. Thus, this pathology can lead to blindness. In order to identify this entity, fundus studies must be performed in preterm infants, who are at risk of suffering it.(39)

The incidence of retinopathy will be measured as a dichotomous nominal qualitative variable and will be described as a proportion.

- Incidence of **Pneumothorax.**

Description: A pneumothorax is a collapsed lung. Pneumothorax occurs when air leaks into the space between your lungs and chest wall. This air pushes on the outside of your lung and makes it collapse. In most cases, only a portion of the lung collapses. A pneumothorax is generally diagnosed using a chest X-ray. In some cases, computerized tomography (CT) scan may be needed to provide more detailed images.(40)

The incidence of this pathology will be measured as a dichotomous nominal qualitative variable and will be described as a proportion.

Covariates

- Gestational Age: Gestational age is the common term used during pregnancy to describe how far along the pregnancy is. It is measured in weeks, from the first day of the woman's last menstrual cycle to the current date. A normal pregnancy can range from 38 to 42 weeks. Infants born before 37 weeks are considered preterm. It will be measured as a continuous ordinal quantitative variable and described as a mean ± standard deviations.

- Birth weight: It will be measured as a continuous quantitative variable and described as a mean ± standard deviations.

- Gender: It will be measured as a dichotomous nominal qualitative variable and described as a proportion.
- Complete antenatal corticosteroids: It will be measured as a dichotomous nominal qualitative variable and described as a proportion.
- APGAR 1min and 5min: It will be measured as a nominal qualitative variable and described as a proportion.

FIGURE 9: APGAR SCORE(41)

APGAR SIGN	2	1	0
Heart Rate (pulse)	Normal (above 100 beats per minute)	Below 100 beats per minute	Absent (no pulse
Breathing (rate and effort)	Normal rate and effort, good cry	Slow or irregular breathing, weak cry	Absent (no breathing)
Grimace (responsiveness or “reflex irritability”)	Pulls away, sneezes, coughs, or cries with stimulation	Facial movement only (grimace) with stimulation	Absent (no response to stimulation
Activity (muscle tone)	Active, spontaneous, movement	Arms and legs flexed with little movement	No movement, “floopy” tone
Appearance (skin coloration)	Normal colour all over (hands and feet are pink)	Normal colour (but hands and feet are bluish)	Bluish-grey or pale all over

❖ **Data collection**

Personal from the NICUs of the hospitals involved in the study, previously informed, coordinated and trained for this clinical trial will work together for data collection following specific tables (see ANNEX 3). Just after birth neonatologist will fill in Table 1. Then, all events will be registered in the history of the patient by physicians and nurses, 72h after birth Table 2 will be filled in excepting those questions with no data registered. Right before finishing the follow up of the patient needed for the study Table 2 will be correctly completed.

A statistical in practices will carry out a monitoring of the data registered in the history of the patients in order to provide the most accurate information for the results. The data will be classified in centers, in order to be able to analyze the results of each hospital independently.

❖ **Other activities from the study**

Apart from the tasks of the study, this project will include the following meetings:

- **Meeting 1:** Study coordinator (SC), Neonatologists (Neos) and Statistical specialist (SS).
  - The main aim of this meeting is to elaborate the protocol design from the first draft and the bibliography research carried out by the SC and to define the collaborator groups and task distribution.
- **Formation course:** SC and Neos.
  - The aim of the course is to train he physicians how to reproduce both surfactant administration methods of the study in order to realize the same procedures in all the centers involved.
  - The course will be given by the neonatologists Alberto Trujillo and Mario Sanchez, form HUDJT, who have a large experience and are highly qualified to perform both procedures.
  - The reunion will take place in HUDJT with the help of infant intubable dummies and the instruments needed to perform both techniques.
  - It will be composed of one hour of theory and then one hour and a half of practice. We will divide the Neos into four groups for the practice part: two groups will attend the first turn, one for each professional, and the other two groups will attend the second turn.
- **Meeting 2 and 3:** SC, Neos, Nurses unrelated to child care (Nuc) and SS.

- The second meeting will be 12 months after the data collection start and the third one will be after 24 months. The aim is to identify if there is any remarkable error on the data collection and on the results obtained.
- In case any shocking result is identified with the help of the SS, the importance of stopping the project will be studied.

- **Meeting 4:** SC, Neos and SS.
  - The meeting will take place after the statistical analysis and the results will be edited.
  - A program for publication and dissemination of the results will be designed.

The four meetings will take place in an adapted space in *Hospital Maternoinfantil Sant Joan de Déu*, taking into account that the majority of the centers involved are closer to the mentioned place; so that the collaborators will have easier access and it will reduce costs.

❖ **Task and research team**

The collaborators list and the tasks assigned to each group of professionals are described as follows:

- **Study coordinator:** Judith Serrat
  - Coordination of the study.
  - Bibliography research.
  - First draft of the protocol design.
  - Study participation including data collection.
  - Interpretation of the results and dissemination through conferences.
- **Neonatologists:** Between 6 and 8 physicians per center will be trained and will participate in the study (depending on the center) but only 2 neonatologists per center will attend the meetings.
  - Final protocol design (by the ones attending the meetings).
  - Recruitment.
  - Treatment of the patient including surfactant administration.
  - Data collection.
- **Nurses:** Between 6 and 8 nurses per center. Two nurses per center will attend the meetings in order to receive indications for data collection so that all centers will do it the same way, then they will transmit the information to other nurses involved.
  - Children care.
  - Data collection.

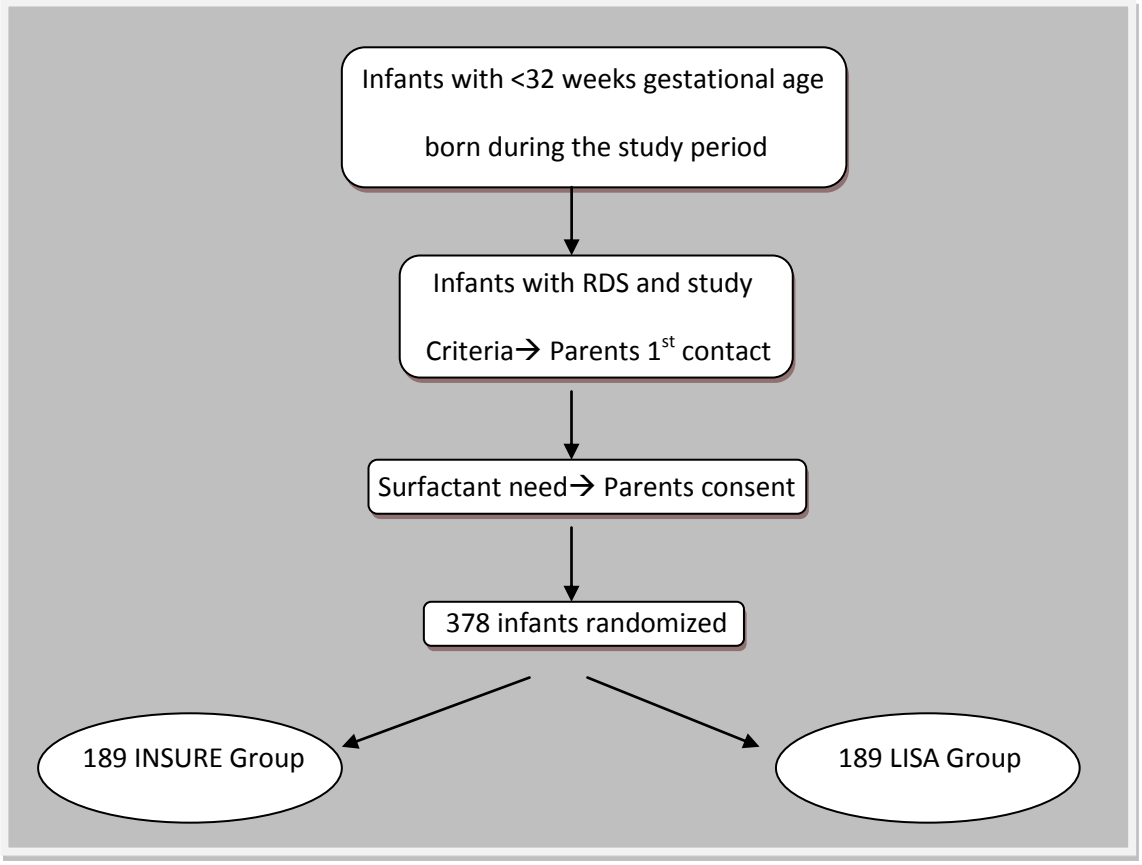
- **Statistical specialist:**
  - Randomization programme design.
  - Monitoring and quality control of data collection.
  - Statistical analysis.

Apart from the statistical specialist, all professionals described have accepted to participate in this study voluntarily and without any reward.

The centers involved have also allowed the use of their facilities and equipments.

All the collaborators are highly qualified to perform the tasks described and their large experience must be mentioned.

Summary of the progress



7. STATISTICAL ANALYSIS

The univariate analysis of the qualitative variables will be done using proportions while the analysis of the quantitative variables will be performed using the mean ± SD if they have a normal distribution and if not, median will be used.

Considering the bivariate analysis, the efficacy analysis will be done using relative risk estimation, with 95% confidence interval. To prove statistical association between the intervention and qualitative variables a $\chi 2$ test (Pearson's chi-square test) will be applied.

An Odds Ratio will be used to analyze mortality and the primary dependent variable, MV after 72h.

A multivariate analysis will be performed using a Cox proportional hazards model to evaluate the contribution of covariates (gender, gestational age, complete antenatal corticosteroid maturation, APGAR).

Data will be recorded on computer database using the software Microsoft Excel. All statistical analyses will be carried out using the Statistical Package for the Social Science (SPSS), version 22.0, and all tests will be considered statistically significant at a p value ≤ 0.05.

8. LIMITATIONS

Analyzing our study, we detected and took into account some limitations which interfere in the research. The most relevant limitations are explained below:

1. Due to the need of knowing the technique to be performed in each patient, this study cannot be blinded. But patients' care will always be according to clinic guides. Thus, differences among the two patient groups and interferences in the results will be reduced.

Moreover, we use strong objective variable to prove the effectiveness of the intervention and we blind the data collected to the statistical specialist responsible to perform the statistical analysis, thus he/she will not know which results match to each technique.

2. LISA technique will be standardized in the formation course, but the way of intubation in the INSURE group (nasal or oral) will depend on each physician. Although it means that patients could be treated in a different way, we consider that it has minim effects on the results and that standardize a unique intubation way could interfere in the rate of success of the technique.

3. Preterm deliveries cannot be expected, so that, we need neonatologists involved in the study in every shift in order to have professionals enough to cover all patients with criteria to join our study. This fact also means that there will be a lot of physicians collecting data for the study; in order to minimize the errors committed in the data collection period a statistic professional will be hired to make a monitoring and quality control of the information.

4. Due to the stressful situation that parents will be going through, we assume that the participation rate will be very low, so that we have enlarged the recruitment period to cover the sample size needed.

5. The cost of the project is quite expensive due to the pattern of the surfactant (425€ per dose).

6. Complete prenatal corticosteroids can make the difference in the prognosis of the patients with RDS; that fact could lead to a bias on our results of the techniques, but the randomization process we performed in the study will try to avoid this bias.

7. The results of our study will be extrapolated to extremely preterm infants with RDS, but according to our participation criteria we will not be able to specify in which group of patients the technique has the better benefits, as we include children from 24-32 gestational weeks. If the results are the ones expected, more accurate studies should be performed.

9. ETHICAL ASPECTS

This study will be conducted according to the ethical principles established by World Medical Association in the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects. The research protocol must be presented and submitted for consideration, guidance and approval by the *Clinical Research Ethical Committee at Hospital Universitari Doctor Josep Trueta*, and also in the other mentioned centers involved in the study, before it begins, and at the end of the study. The final report must also be submitted to the CREC after the study's ending.

According to *Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal*, personal and clinical information of all participants will be confidential and only used for research purpose. Moreover, all data will be analyzed anonymously. All parents of the participants will be personally informed by researchers and an information document about the study will be given to them (see ANNEX 1), then they will have to sign voluntarily the informed consent (see ANNEX 2), according to "Ley 41/2002 Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".

According to Nüremberg Code (1947) each candidate to join a clinical trial must have legal and real capacity to give his/her consent, and the patient must be in conditions which allow the free choice exercise, without pressure, fraud, deception or coercion. The stressful situation parents will face must be taken into account. They must be informed and not coerced and they must sign the acceptance of taking part in the study voluntarily, and understanding all the items explained in the patient information sheet.

We have evaluated the need of an intermediate analysis, which would require adjustments for multiple comparisons and a wider sample size, in order to stop the study if there are recorded evidences pointing a much better effectiveness of one of the techniques used. We have discarded it, but if during the meetings relevant findings are found, the possibility of stopping the study will be discussed. However, the security will be evaluated continuously during this clinical trial, the appearance of adverse events, in either of the techniques, which could compromise the integrity of the patients, would represent the immediately stop of the study. Moreover, it would be reported and published.

10. WORK PLAN AND CHRONOGRAM

❖ Work plan

The research team will be composed of: one study coordinator (**SC**), neonatologists (**Neos**), nurses unrelated to child care (**Nuc**) and one statistical specialist (**SS**).

The duration of the present clinical trial will last approximately three years and nine months (45 months), including the protocol elaboration, execution and publication. It will be organized according the following steps:

TASK 1: PREPARATION AND COORDINATION PHASE

1. Protocol design (**3 months**): During this first period the initial idea and protocol will be designed. The SC will have the functions of initiating, managing and ensuring the funding and resources for the study.
2. Coordination of the centers and members of the study (**3 months**): Selection of the centers that will be enrolled in the study. The protocol will be discussed with the members of the study in order to make sure that all the procedures are accepted. Finally, the Clinical Research Ethics Committee from each center will evaluate and approve the protocol.
3. Meeting 1: SC, Neos and SS will attend the first meeting. Explained in *Other activities of the study.*
4. Formation Course: A formation course will be given to the Neos. The aim of the course is to let them know the techniques used in the study (INSURE and LISA) in order to make sure that there are no differences between the different centers of the study. Explained in *Other activities of the study* in more detail.

TASK 2: FIELD WORK AND DATA COLLECTION

5. Study and data collection (**30 months**): Patient recruitment, randomization and data collection. The duration of the study will last 2 years and six months: time for the recruitment, data collection and follow up (its length can be modified according to the needs; the objective is to enroll 378 patients). During this phase the following activities will be done:
   - Nuc: Usual care of the preterm. Data collection.
   - Neo: Surfactant administration and follow up of the patient. Data collection.
6. Meeting 2 (**12 months after initiate data collection**) and meeting 3 (**24 months after initiate data collection**): SC, Neos and SS will attend the second and third meeting. Explained in

Other activities of the study. After the third meeting the sample recruitment should be finished.

TASK 3: DATA ANALYSIS AND FINAL EVALUATION

7. Statistical Analysis: It will be done by the SS.
   - Preparation of the randomization. Design the statistical software to carry out the probability sampling.
   - Monitoring and quality control of data during all the study.
   - Assessed interim analysis, in the 100, 200, 300 enrolled infants with the finality to stop the clinical trial if there was any relevant problem.
   - Final statistical analysis (**3 months**): Data of the 378 infants will be analyzed.
8. Meeting 4 (**after statistical analysis**): SC, Neos and SS will attend the fourth meeting. Explained in *Other activities of the study.*

TASK 4: PUBLICATION AND DISSEMINATION

9. Publication and dissemination of the results (**6 months**): writing and edition of the results. Publication. Finally the SC will attend conferences in order to disseminate the findings.

❖ **Chronogram**

STUDY TASKS	2015	2016				2017				2018				2019	
	Oct-Des	Jan-Mar	April-June	July-Sept	Oct-Des	Jan-Mar	April-June	July-Sept	Oct-Des	Jan-Mar	April-June	July-Sept	Oct-Des	Jan-Mar	April-June
TASK 1: PREPARATION AND COORDINATION PHASE															
Protocol elaboration															
Coordination of the research team and training															
CREC evaluation															
TASK 2: FIELD WORK AND DATA COLLECTION															
Patient recruitment															
Data collection															
Follow up of the patient															
TASK 3: DATA ANALYSIS AND FINAL EVALUATION															
Monitoring and quality control of data															
Statistical analysis															
Interpretation of the results															
Final report elaboration															
TASK 4: PUBLICATION AND DISSEMINATION															
Publication															
Congresses attendance															

11. BUDGET

Means available:

The research team is employed by the institution and it is not required to work overtime, for this reason, these services are not included in our budget.

As the study will be carried out in four hospitals with NICUs level III, all equipment required for the follow up of the patients will be provided by these centers. Furthermore, the tests done to each patient, as they relate to routine tests of the preterm infant, will be realized in every of the centers involved with none extra cost in the study's budget.

Means needed and included in the budget:

The research team does not have enough knowledge to perform the statistical analysis. Therefore we will hire a statistical service. A skilled staff is also required to carry out the monitoring and quality control of the data collected (2h/week). Both services are included in our budget.

Although we are testing the effectiveness of the administration technique and not of the surfactant, we will provide the mentioned drug in order to use the same in each patient and avoid a possible bias in the results. As well as we do not intent to benefit any pharmaceutic business.

(1) We have estimated 450 doses of surfactant. It is necessary to administrate 378 doses (one for each patient) and we estimate a 20% extra for those children who need a second and third surfactant administration.
(2) We have estimated 230 endotracheal tubes. One tube for each patient of the INSURE Group and a 20% extra for second and third administrations when required.
(3) We have estimated 230 catheters. One for each patient of the LISA Group and a 20% extra for second and third surfactant administration when needed.
(4) Other services include printing information sheets for patients, informed consent forms and participant data sheets.
(5) The space rental includes a classroom with audiovisual player. HUDJT has offered this service to us, as well as the material need during the tutorial, in order to encourage physicians to perform studies.
(6) Equipment includes: infant intubable dummies, endotracheal tubes, catheters, laryngoscope, Magyll forceps, ambus or respiratory support equipment.
(7) The cost of the insurance policy is an approximate cost done from the information obtained from an insurance company named *Confide Correduría de Seguros y Reaseguros S.A*. (see ANNEX 4)

		BUDGET PROPOSAL		
		Quantity	Cost per unit	Cost
SERVICES	Statistical Specialist	90h	35€/h	3.150€
	Monitoring and data quality control	2h/week= 264h	30€/h	7.920€
DRUGS	Curosurf® Poractant Alfa	450 doses [1]	425€	191.250€
GOODS AND SERVICES	Endotracheal tube (double lumen)	230 units[2]	2€	460€
	Catheters	230 units[3]	0.5€	115€
	Other services[4]	1	50€	50€
MEETINGS	Transport and meals	56	50€/person	2.800€
FORMATION COURSE	Transport and meals	31	50€/person	1.550€
	Space rental[5]	At the expense of Hospital Universitari Doctor Josep Trueta		
	Equipment[6]			
	Professional services (Dr. Alberto Trujillo and Dr. Mario Sanchez)	2x4h=8h	50€/h	400€
INSURANCE	Insurance policy[7]	1	30.000€	30.000€
PUBLICATION	Cost of publication	1	2.500€	2.500€
DISSEMINATION	National journey	1	1.000€	1.000€
	International journey	1	2.000€	2.000€
		TOTAL COST		**243.195€**

12. CONFLICT OF INTEREST

The authors declare no conflicts of interest.

13. IMPACT OF THE PROJECT

If the results obtained are the ones expected; with significant relevance and with the validation of our hypotheses, we consider that LISA techniques could be introduced immediately and without complications in the daily clinical practice, and this would lead to a big improvement in the medical aspect.

On the one hand, minimal invasive procedures would improve the recovery and the prognosis of those patients who are in a situation of vulnerability. They could avoid aggressive procedures and this is an important point to have into consideration taking always into account the patient's care and security. Furthermore, LISA technique is much less expensive to reproduce and needs less equipment.

On the other hand, if the hypotheses are validated, and the incidence of BPD is reduced, medical costs could also be reduced avoiding the expenses of treating this pathology.

However, further research is required to confirm possible findings and to revalidate the results. With increasing knowledge in this field, perinatal medicine may be improved significantly.

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15. ANNEX

❖ **ANNEX 1: Information Sheet**

FULL INFORMATIU PEL PACIENT

ADMINISTRACIÓ DE SURFACTANT MITJANÇANT TÈCNIQUES NO INVASIVES RESPECTE TÈCNIQUES INVASIVES CONVENCIONALS EN PACIENTS PREMATURS DE MENYS DE 32 SETMANES DE GESTACIÓ: ASSAIG CLÍNIC RANDOMITZAT MULTICÈNTRIC

Estudi multicèntric, randomitzat en dos grups, en relació amb el maneig del Síndrome de Distrés Respiratori del prematur, ambdós grups es tractaran amb surfactant variant la tècnica d'administració: un grup es tractarà mitjançant una sonda amb suport respiratori no invasiu, l'altre grup mitjançant intubació convencional.

Benvolgut,

Ens dirigim a vostè per convidar-lo a permetre la participació del seu nadó en un estudi de recerca que s'està portant a terme a la Unitat de Neonatologia de diferents hospitals de Catalunya sobre el maneig del Síndrome de Distrés Respiratori del Preterme. Es pretén investigar una tècnica menys invasiva per l'administració del fàrmac necessari per tractar aquesta patologia (Surfactant).

Abans que prengui la decisió de participar o no en aquest estudi, és imprescindible que llegeixi i entengui aquest full informatiu i, davant de qualsevol dubte, pregunti al doctor que li convida participar en l'estudi.

Participació voluntària:

És important que sigui conscient que participar a l'estudi és voluntari i que pot no fer-ho, canviar d'opinió o retirar el seu consentiment informat si ho desitja, sense que això alteri la seva relació amb el seu metge ni es produeixi cap perjudici en el seu tractament. Per tal que pugui prendre la millor decisió, li proporcionem la informació correcta i suficient per a que pugui valorar-ho adequadament.

Descripció de l'estudi:

El grup de professionals destinats a la investigació d'aquest estudi són especialistes en pediatria i en nounats, i en les complicacions relacionades a la prematuritat.

L'estudi es centra en aquells nadons nascuts amb una edat gestacional de menys de 32 setmanes que presentin Síndrome del Distrés Respiratori del prematur. El protocol actual considera que se'ls ha d'administrar Surfactant mitjançant tècniques INSURE, que consisteixen en intubar el nadó,

administrar el surfactant i extubar. Aquest procediment es realitza sota sedació prèvia. Actualment, altres tècniques d'administració d'aquest medicament estan en estudi i resulten menys invasives. El que es proposa en aquest assaig clínic és administrar el fàrmac mitjançant una sonda a través de les cordes vocals fins a la tràquea, sense necessitat de ventilació mecànica.

L'objectiu de l'estudi és comprovar si mitjançant tènciques mínimament invasives es redueix la necessitat de ventilació mecànica (VM) i altres possibles complicacions en el prematur extrem, com la incidència de Broncodisplàsia Pulmonar.

Grups de tractament:

Hi haurà dos grups de tractament, seleccionats aleatòriament una vegada hagin firmat el consentiment informat.

- Grup 1: es tractarà amb una dosi de 200mg/dl de surfactant mitjançant tècnica INSURE. Previ al tractament s'administrarà cafeïna per evitar apnees i bradicàrdies i sedoanalgèsia segons l'opinió professional per evitar el dolor i molèsties de la pròpia tècnica.
- Grup 2: es tractarà amb una dosi de 200mg/dl de surfactant mitjançant una sonda introduïda a través de les cordes vocals fins a la tràquea. Es donarà suport ventilatori nassal no invasiu. Igualment s'administrarà cafeïna per mantenir la respiració espontània del nadó i prevenir apnees i bradicàrdies. La sedació es realitzarà sota criteri del professional mèdic segons les condicions dels pacients.

Interrupció de l'estudi:

Vostè podrà abandonar l'estudi quan ho consideri oportú o necessari, ja sigui per motius personals com mèdics; per patir esdeveniments adversos greus; si no es compleix amb la *"Ley del Medicamiento"* o amb els principis ètics del Reial Decret 223/2004. Abans de prendre dita decisió, seria convenient que parlés amb el doctor/a que li ha ofert participar en l'estudi.

Beneficis:

Esperem trobar el millor maneig pel Distrés Respiratori del Prematur per tal de disminuir les diferents complicacions que aquests nadons poden patir.

Riscos:

En cas que la tècnica assignada no es pugui realitzar correctament per les condicions del pacient, es procedirà a realitzar una altra tècnica, segons la pauta clínica establerta, tenint sempre com a prioritat el benestar del pacient.

Responsabilitat i assegurança:

El doctor/a responsable de l'estudi ha contractat una assegurança que cobreix la responsabilitat legal per danys ocasionats a les persones que hi participen i als derivats d'aquesta investigació, realitzada conforme el protocol científic i la legislació vigent.

Confidencialitat:

La informació mèdica, i qualsevol informació recollida sobre el seu nadó durant l'estudi, seran confidencials, en cap cas el seu nom apareixerà en la publicació dels resultats.

La seva privacitat està protegida i recollida en la Llei Orgànica 15/1999 sobre Protecció de Dades personals i el corresponent Reial Decret Nacional 1720/2007.

Compensació econòmica:

La participació en aquest estudi no serà beneficiaria de cap compensació econòmica.

En cas de generar-se un desenvolupament comercial dels coneixements obtinguts, els possibles beneficis seran destinats a cobrir costos científics.

Consentiment informat:

En el cas que vostè decideixi donar autorització per formar part d'aquest assaig clínic, haurà de firmar el següent consentiment informat per tal d'evidenciar que coneix les condicions de l'estudi i les accepta.

HOJA INFORMATIVA PARA EL PACIENTE

ADMINISTRACION DE SURFACTANT MEDIANTE TÉCNICAS NO INVASIVAS RESPETO TÉCNICAS INVASIVAS CONVENCIONALES EN PACIENTES PREMATUROS DE MENOS DE 32 SEMANAS DE GESTACIÓN: ENSAYO CLÍNICO RANDOMIZADO MULTICÉNTRICO

Estudio multicéntrico, randomizado en dos grupos, en relación con el manejo del Síndrome de Distrés Respiratorio del prematuro, ambos grupos se trataran con surfactante cambiando la técnica de administración: un grupo se tratará mediante una sonda con soporte respiratorio no invasivo, el otro grupo mediante intubación convencional.

Bienvenido,

Nos dirigimos a usted para invitarlo a permitir la participación de su hijo en un estudio que se está llevando a cabo en las Unidades de Neonatología de diferentes hospitales de Cataluña sobre el manejo del Síndrome de Distrés Respiratorio del Pretérmino. Se pretende investigar una técnica menos invasiva para la administración del fármaco necesario para tratar esta patología (Surfactante).

Antes de tomar la decisión de participar o no en este estudio, es imprescindible que lea y entienda esta hoja informativa y, ante cualquier duda, pregunte al doctor que le invita a participar en el estudio.

Participación voluntaria:

Es importante que sea consciente que participar en el estudio es voluntario y que puede no hacerlo, cambiar de opinión o retirar su consentimiento si lo desea, sin que esto altere su relación con su médico ni se produzca ningún perjuicio en su tratamiento. Para que pueda tomar la mejor decisión, le proporcionamos la información correcta y suficiente para que pueda valorarlo adecuadamente.

Descripción del estudio:

El grupo de profesionales destinado a la investigación de este estudio son especialistas en pediatría y neonatos, y en las complicaciones relacionadas con la prematuridad.

El estudio se centra en aquellos neonatos nacidos con una edad gestacional de menos de 32 semanas que presenten Síndrome de Distrés Respiratorio del prematuro. El protocolo actual considera que se les debe administrar Surfactante mediante técnicas INSURE, que consisten en intubar al paciente, administrar el surfactante y extubar. Este procedimiento se realiza bajo sedación previa. Actualmente, otras técnicas de administración de este fármaco están en estudio y resultan menos

invasivas. Lo que propone este ensayo clínico es administrar el medicamento mediante una sonda a través de las cuerdas vocales hasta la tráquea, sin necesidad de ventilación mecánica.

El objetivo del estudio es comprobar si mediante técnicas mínimamente invasivas se reduce la necesidad de ventilación mecánica (VM) y otras posibles complicaciones en el prematuro extremo, como la incidencia de Broncodisplasia Pulmonar.

Grupos de tratamiento:

Habrá dos grupos de tratamiento, seleccionados aleatoriamente una vez hayan firmado el consentimiento informado.

- Grupo 1: se tratará con una dosis de 200mg/dl de surfactante mediante técnica INSURE. Previo al tratamiento se administrará cafeína para evitar apneas y bradicardias y sedoanalgesia según la opinión del profesional para evitar el dolor y molestias de la propia técnica.
- Grupo 2: se tratará con una dosis de 200mg/dl de surfactante mediante una sonda introducida a través de las cuerdas vocales hasta la tráquea. Se dará soporte ventilatorio nasal no invasivo. Igualmente se administrará cafeína para mantener la respiración espontánea del niño y prevenir apneas y bradicardias. La sedación se realizará bajo el criterio del profesional médico según las condiciones de los pacientes.

Interrupción del estudio:

Usted podrá abandonar el estudio cuando lo considere oportuno o necesario, ya sea por motivos personales como médicos; por padecer acontecimientos adversos graves; si no se cumple con la *"Ley del Medicamiento"* o con los principios éticos del Real Decreto 223/2004. Antes de tomar dicha decisión, sería conveniente que hablase con el doctor/a que le ha ofrecido participar en el estudio.

Beneficios:

Esperamos encontrar el mejor manejo para el Distrés Respiratorio del Prematuro con la finalidad de disminuir las diferentes complicacions que estos recién nacidos pueden padecer.

Riesgos:

En caso que la técnica asignada no se pueda realizar correctamente por las condiciones del paciente, se realizará otra técnica, según la pauta clínica establecida, teniendo siempre como prioridad el bienestar del paciente.

Responsabilidad y seguro:

El doctor/a responsable del estudio ha contratado un seguro que cubre la responsabilidad legal para daños ocasionados a las personas que participen y a los derivados de esta investigación, realizada conforme el protocolo científico i la legislación vigente.

Confidencialidad:

La información médica, y cualquier información recogida sobre su hijo durante el estudio, serán confidenciales, en ningún caso su nombre aparecerá en la publicación de los resultados.

Su privacidad está protegida y recogida en la Ley Orgánica 15/1999 sobre Protección de Datos personales y su correspondiente Real Decreto Nacional 1720/2007.

Compensación económica:

La participación en este estudio no será beneficiaria de ninguna compensación económica.

En caso de generarse algún desarrollo comercial de los conocimientos obtenidos, los posibles beneficios serán destinados a cubrir gastos científicos.

Consentimiento informado:

En el caso que usted decida dar autorización para formar parte de este ensayo clínico, tendrá que firmar el siguiente consentimiento informado para evidenciar que conoce las condiciones del estudio y las acepta.

❖ **ANNEX 2: <u>Informed consent</u>**

FORMULARI DE CONSENTIMENT INFORMAT

ADMINISTRACIÓ DE SURFACTANT MITJANÇANT TÈCNIQUES NO INVASIVES RESPECTE TÈCNIQUES INVASIVES CONVENCIONALS EN PACIENTS PREMATURS DE MENYS DE 32 SETMANES DE GESTACIÓ: ASSAIG CLÍNIC RANDOMITZAT MULTICÈNTRIC

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Jo (nom i cognoms) _____ en qualitat de _____ (relació amb el participant) de _____ (nom i cognoms del participant)

He llegit la fulla d'informació que m'ha estat entregada.

He pogut fer preguntes sobre l'estudi en qüestió.

He rebut suficient informació sobre l'estudi.

He parlat amb: _____ (nom de l'investigador).

Entenc que la participació és voluntària.

Entenc que puc retirar el meu consentiment de participació:

- Quan ho desitgi.
- Sense necessitat de donar explicacions.
- Sense que tingui repercussions en la cura mèdica.

Dono la meva conformitat per tal que _____(nom del participant) participi en aquest estudi i dono el meu consentiment per l'accés i utilització de les dades en les condicions detallades en el full d'informació al pacient.

FIRMA TUTOR O REPRESENTANT LEGAL **FIRMA INVESTIGADOR**

FORMULARIO DE CONSENTIMIENTO INFORMADO

ADMINISTRACION DE SURFACTANT MEDIANTE TÉCNICAS NO INVASIVAS RESPETO TÉCNICAS INVASIVAS CONVENCIONALES EN PACIENTES PREMATUROS DE MENOS DE 32 SEMANAS DE GESTACIÓN: ENSAYO CLÍNICO RANDOMIZADO MULTICÉNTRICO

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Yo (nombre y apellidos) _____ en calidad de _____ (relación con el participante) de _____(nombre y apellidos del participante)

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio en cuestión.

He recibido suficiente información sobre el estudio.

He hablado con: _____ (nombre del investigador).

Entiendo que la participación es voluntaria.

Entiendo que puedo retirar mi consentimiento de participación:

- Cuando lo desee.
- Sin necesidad de dar explicaciones.
- Sin que tenga repercusiones en los cuidados médicos.

Doy mi conformidad para que _____ (nombre del participante) participe en este estudio y doy mi consentimiento para el acceso i utilización de los datos en las condiciones detalladas en la hoja de información al paciente.

FIRMA TUTOR O REPRESENTANTE LEGAL **FIRMA INVESTIGADOR**

❖ **ANNEX 3: Data collection**

TABLE 1

PARTICIPANT CODE: _____

GROUP: ☐ A ☐ B

- **Gestational Age** (weeks + days): _____
- **Gender**: ☐ Female ☐ Male
- **Height** (cm): _____ **Weight** (gr): _____
- **Complete antenatal corticosteroids**: ☐ Yes ☐ No
- **1min Apgar Score**: _____
- **5min Apgar Score**: _____
- **FiO_2 prior to surfactant administration**: _____
- **PEEP prior to surfactant administration**: _____

TABLE 2

PARTICIPANT CODE: _____

GROUP: ☐ A ☐ B

- **Need of MV 72h:** ☐ Yes ☐ No
  - **Days:** _____
- **Need of MV during study:** ☐ Yes ☐ No
  - **Days**: _____
- **Need of nCPAP** (days): _____
- **Need of oxygen** (days): _____
- **Diagnosis of BPD:** ☐ Yes ☐ No
  - **Grade:** ☐ Mild
    ☐ Moderate
    ☐ Severe
- **Diagnosis of PDA:** ☐ Yes ☐ No
  - **Grade:** ☐ Need of treatment
    ☐ Not need of treatment
- **Diagnosis of NEC:** ☐ Yes ☐ No
  - **Grade:** ☐ Ia ☐ Ib
    ☐ IIa ☐ IIb
    ☐ IIIa ☐ IIIb
- **Diagnosis of HIV:** ☐ Yes ☐ No
  - **Grade:** ☐ GI
    ☐ GII
    ☐ GIII
    ☐ GIV
- **Diagnosis of Retinopathy:** ☐ Yes ☐ No
  - **Grade:** ☐ Need of treatment
    ☐ Not need of treatment
- **Diagnosis of Pneumothorax:** ☐ Yes ☐ No
- **Exitus:** ☐ Yes ☐ No

ANNEX 4: Insurance information

Buenas tardes Sra. Serrat,

Sin documentación nos es imposible dar un precio para un ensayo, ya que depende de muchas variables y de las tarifas de cada compañía.
Dado que no es para ningún ensayo de verdad y que es sólo para el proyecto de fin de grado y a título orientativo este ensayo tendría un coste mínimo de 12.000€, el máximo iría en función de las variables y tarifas arriba indicadas, pero tratándose de prematuros se puede encarecer bastante y podría elevarse a 30.000€ o más.

No sé si le he sido de mucha ayuda pero dar un precio de un ensayo sin más datos sólo puede ser muy orientativo.

Reciba un cordial saludo.

Blanca Martínez
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