TREBALL FINAL DE GRAU
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# IV paracetamol versus IV ibuprofen for the treatment of PDA in LBW infants: a randomized controlled trial.

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This protocol could not have been done without the knowledge provided by Mª Angels Puigdevall and Susana Uriel, pediatric cardiologists.

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## 1 LIST OF ABREVIATIONS

| | |
|---|---|
| **AEMPS** | Asociación Española de Medicamentos y Productos Sanitarios |
| **BPD** | Bronchopulmonary dysplasia |
| **COX** | Cyclooxygenase inhibitors |
| **DA** | Ductus arteriosus |
| **hsPDA** | Hemodynamically significant PDA |
| **HUJT** | Hospital Universitari Josep Trueta |
| **HUVH** | Hospital Universitari Vall d´Hebron |
| **IV** | Intravenous |
| **IVH** | Intraventricular hemorrhage |
| **LA/Ao** | Left atrium to aortic root ratio |
| **LBW** | Low birth weight |
| **NCPAP** | Nasal continuous positive airway pressure |
| **NEC** | Necrotizing enterocolitis |
| **NSIMV** | Nasal synchronized intermittent mandatory ventilation |
| **PDA** | Patent ductus arteriosus |
| **PGE2** | Prostaglandin E2 |
| **PGI2** | Prostacyclin |
| **PIH** | Pregnancy induced hypertension |
| **POX** | Peroxidase |
| **PVL** | Periventricular leukomalacia |
| **SIMV** | Synchronized intermittent mandatory ventilation |

## 2 ABSTRACT

Patent ductus arteriosus is a prevalent problem in low birth weight infants and it has an important morbidity and mortality in this group of patients. Classical treatment options include drugs (intravenous cyclooxygenase inhibitors: indomethacin and ibuprofen) and surgical ligation, but these treatments are associated with significant adverse effects. An alternative treatment with fewer side effects is needed. The role of oral paracetamol has gained importance in recent years, this new therapeutic option is being widely studied, and there are already many studies which support oral paracetamol as first line treatment for PDA, due to its better safety profile than classical drugs. In LBW infants is difficult to administer enteral treatment, since they are often multi pathological patients with several complications that preclude oral administration and they usually receive intravenous treatments. This multicenter, prospective, single blinded, randomized, controlled, parallel-group and non-inferiority trial is designed to evaluate the efficacy and safety of intravenous paracetamol versus intravenous ibuprofen in the treatment of PDA in LBW infants. Sixty eight infants with echocardiography confirmed PDA will be randomly assigned to receive either intravenous paracetamol or intravenous ibuprofen. The main endpoints will be the rate of ductal closure of each drug and adverse events in each group of treatment.

**Key words**: Intravenous paracetamol, intravenous ibuprofen, patent ductus arteriosus, low birth weight, controlled trial.

# 3 INTRODUCTION

Patent ductus arteriosus (PDA) is a prevalent problem in low birth weight (LBW) infants and it has an important morbidity and mortality in this group of patients. Classical treatment options include drugs (intravenous cyclooxygenase (COX) inhibitors: indomethacin and ibuprofen) and surgical ligation, but these treatments are associated with significant adverse effects. An alternative treatment with fewer side effects is needed. A new therapeutic option is being widely studied in recent years: oral paracetamol; there are already many studies which support oral paracetamol as first line treatment for PDA, due to its better safety profile than classical treatments. In LBW infants is difficult to administer enteral treatment, since they are often multi pathological patients with several complications that preclude oral administration; they usually receive intravenous (IV) treatments. The current trial is designed to test the hypothesis that IV paracetamol is at least as effective as traditional therapies for the treatment of PDA, producing fewer side effects.

## 3.1 Overview of PDA

Ductus arteriosus (DA) is a vascular structure which connects the descendent proximal aorta with the main pulmonary artery near the origin of the left pulmonary branch. It serves to divert ventricular flow away from the lungs and direct it to the placenta in fetal life. Although patency of the ductus is necessary for fetal circulation, postnatal ductal closure is vital for postnatal circulatory adaptation *(Hamrick et al.)*. If postnatal ductal closure doesn´t happen in first days of life, it keeps the newborn vulnerable to pulmonary overcirculation and diminished systemic blood flow, with consequent complications *(Hammerman et al.).*

The incidence of PDA is inversely proportional to gestational age and birth weight. The incidence in term infants has been estimated to be 57/100.000 live births, whereas in preterm infants weighing 501 to 1500 g (very low birth weight) it has been estimated to be 31%. In addition, 55% of infants who weigh 1000 g or less (extremely low birth weight) have been described as having symptomatic PDA that ultimately requires medical treatment *(Yang et al.).*

Mechanisms that regulate physiologic closure of the PDA depend of its histology. The medial layer of the DA is composed of smooth muscle fibers and elastic tissue, and the intimal layer is composed of smooth muscle and endothelial cells. The DA smooth muscle cell is the site of

oxygen-sensing, and the endothelium segregates vasoactive substances that are important in modulating the DA tone. Fetal patency of DA is regulated by low oxygen tension and elevated prostanoids, predominantly prostaglandin E2 (PGE2) and prostacyclin (PGI2). PGE2 and PGI2 levels are high in the fetus because of placental production and diminished clearance by fetal lungs. After birth at term, a postnatal increase in oxygen concentration and a decrease in circulating vasodilators such as PGE2 and PGI2 will induce constriction of DA smooth muscle cells and closure of the DA in newborns. In preterm infants, the sensitivity for oxygen is reduced, and the sensitivity to vasodilators is increased, all this prevents DA closure. In summary, the mechanisms underlying functional DA closure depend on gestational maturity; the term DA will react to oxygen and decreased concentration of circulating vasodilators by contraction; these sensing mechanisms are altered in preterm infants; thus, anatomic closure may not occur *(Hamrick et al.).*

PDA can have clinical consequences depending on the degree of left-right shunt. The shunt will cause increased pulmonary blood flow and reduction in effective systemic blood flow, and consequently several complications: respiratory decompensation, heart failure, neurologic complications: intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and brain injury, chronic lung disease and bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), renal failure and death. However, although a PDA is associated with these morbidities, its causal role is not clear *(Hamrick et al., Ruiz et al.).*

Ultrasound is the gold standard to diagnose PDA, evaluate its hemodynamic repercussion and establish its severity. Hemodynamically significant PDA (hsPDA) is that which is symptomatic, although clinical signs may not be present early, and in which Doppler ultrasound shows a significant left-right shunt. Clinical signs are not of great value to diagnose a PDA in the early hours, so we can diagnose an hsPDA using just physical signs, but it will be a delayed diagnose, and the preterm infant will be already affected by the complications of the hsPDA; this is why ultrasound is very useful in the diagnosis of hsPDA. With 2D echocardiography, Doppler and color Doppler we can identify the structure, position and size of the ductus, and also identify other cardiac anomalies. (*Golombek et al.*).

Suggestive signs and symptoms of hsPDA are respiratory worsening (increased requirements of $FiO_2$), suggestive murmur and clinical signs of left-right shunt (systolic-diastolic differential

tensions, bounding pulses, metabolic acidosis, cardiomegaly, hepatomegaly, pulmonary edema, pulmonary hemorrhage and hyperdynamic heartbeat) *(Albert)*.

Echocardiographic findings in hsPDA are ductal diameter in 2D echocardiography > 1.4 mm, left atrium to aortic root (LA/Ao) ratio > 1.4, diastolic flow reversal in descending aorta, dilated left cavities and pulsatile ductal flow pattern (Doppler) (*Albert).*

PDA is one of the main factors affecting the survival rate of premature and LBW infants. Consequently, clinical intervention to promote ductal closure is necessary *(Dang et al.).*

### 3.2 Actual therapies for PDA and previous experience

Currently, the first line treatments for PDA are IV COX inhibitors: indomethacin or ibuprofen. These non-steroidal anti-inflammatory drugs promote ductal constriction by inhibiting prostaglandin synthesis. Prostaglandin synthetase has 2 components: a cyclooxygenase (COX) and a peroxidase (POX), that operate at distinct active sites on the same protein with different catalytic activities. COX catalyzes the beginning of prostanoid synthesis from arachidonic acid, at the active COX site arachidonic acid undergoes oxygenation and forms $PGG_2$, which is then acted on by the POX component of the enzyme, forming $PGH_2$. Indomethacin and ibuprofen compete with the arachiconic acid for the active COX site, the potency of these drugs is influenced by endogenous arachidonic acid levels *(Hammerman et al.).*

The clinical trial of *Gimeno et al.,* in 2005, showed that both treatments (IV ibuprofen and IV indomethacin) are equally effective on the closure of hsPDA (87,5% indomethacin versus 82,6 % ibuprofen). Different meta-analysis have reported this similar effectiveness: *Jones et al., Ohlsson et al., Thomas et al. and Gimeno et al.* About safety, it has been demonstrated that complication rate is similar for both drugs: renal complications (transient renal dysfunction, transient renal insufficiency) (9% ibuprofen versus 33% indomethacin); gastrointestinal complications (NEC and perforations) (0% ibuprofen versus 12,5% indomethacin); BPD (30,4 % ibuprofen versus 29,2% indomethacin); among other complications *(Gimeno et al. 2005).* In last years, there are different conclusions among quality meta-analysis about safety of these two drugs: the *Jones et al.* and *Gimeno et al.* meta-analysis find that ibuprofen is related with a highest risk of BPD (30% higher than indomethacin); on the other hand *Ohlsson et al.* and *Thomas et al.* affirm that indomethacin is related with a higher risk of renal affection;

furthermore *Ohlsson et al.* affirms that indomethacin is related with higher risk of NEC. In conclusion, both drugs are equal effective, but they have different complications profile. Despite the existence of quality studies, there are different conclusions about safety, so there is not a consensus about which one to use as first line. The choice of one agent over the other should be based on local availability and dosing preference *(Sivanandan et al.).*

Oral ibuprofen has been studied recently. A randomized controlled trial *(Erdeve et al)* showed that it is as effective and safe as IV ibuprofen for the treatment of hsPDA considering the final success rate of both drugs; although after the first course of treatment PDA closure rate was significantly higher with oral ibuprofen, the need for a second course of ibuprofen was similar between groups. The meta-analysis of *Neumann et* al also reported a similar effectiveness of oral ibuprofen respect to IV COX inhibitors (ibuprofen and indomethacin), without finding differences about side effects. A retrospective study in a single center (*Yang et al.*) also showed the same rates of ductal closure with oral ibuprofen (81,8%) and IV indomethacin (88,5%), with no significant differences regarding side effects or complications.

The role of oral paracetamol as an alternative treatment for hsPDA has gained importance in recent years due to potential effects of classic drugs, and recent studies have shown that it can be used to treat PDA in preterm infants with good efficacy and seemingly few side effects (*Dang et al.*). Paracetamol is a common antipyretic and analgesic drug which also inhibits prostaglandin synthetase activity. Although its mechanism of action remains controversial, paracetamol seems to act at the POX segment of the enzyme. POX is activated at 10-fold-lower peroxide concentrations than is COX. Therefore, paracetamol-mediated inhibition is facilitated at reduced local peroxide concentrations (hypoxia). These differences would permit POX inhibition to be optimally effective under conditions in which COX inhibition is less active (*Hammerman et al.*)

A randomized controlled non-inferiority trial *(Dang et al.)* showed that oral paracetamol was comparable to COX inhibitors as a first line treatment in terms of ductal closure (closing rate with paracetamol 81,2% versus 78,8% with ibuprofen) and even showed a decreased risk of hyperbilirubinemia and gastrointestinal bleeding. Therefore, paracetamol may be accepted as a firs line drug for PDA in preterm infants. Exists another randomized controlled trial (*Oncel et al*. 2014) which compared oral paracetamol with oral ibuprofen and also demonstrated that paracetamol may be a medical alternative in the management of PDA (closing rate paracetamol 77,5% versus ibuprofen 72,5%).

About IV paracetamol, only a study has been published, (*Oncel et al. 2013)* administering IV paracetamol to a series of 10 preterm infants whose feeding was contraindicated or had feeding intolerance. IV paracetamol was used instead of indomethacin or ibuprofen because of possible gastrointestinal side effects of classic drugs (gastrointestinal bleeding, spontaneous perforation, NEC). Results demonstrated a 100% success in ductal closure, but the series was not powered enough to show efficacy of IV paracetamol for hsPDA closure.

### 3.3 Rationale for the need of the study

After publication of *Oncel et al* in 2013, not powered enough to show efficacy of IV paracetamol, the aim of our trial is to evaluate with a clinical trial the efficacy of IV paracetamol versus IV ibuprofen for the closure of hsPDA. Considering the previous experience with oral paracetamol, it seems to be as effective as traditional treatments and have a better safety profile; in LBW infants it would be preferred an IV treatment due to the difficulty of enteral feeding in these patients. If IV paracetamol is indeed proven to be effective, it could become the treatment of choice for the management of hsPDA.

### 3.4 Dose rationale

Subjects will be randomized to one of the following regimens:

IV paracetamol, at the doses of 15 mg/kg every 6 hours during 72 hours (12 doses) *(Oncel et al. 2013).*We will use a solution for perfusion with a concentration of 10 mg/ml (Paracetamol Actavis®).

IV ibuprofen, an initial dose of 10 mg/kg, followed by 2 doses of 5 mg each 24 hours *(Gimeno et al. 2005).* We will use a solution for perfusion with a concentration of 10 mg/ml (Neoprofen®).

At present IV paracetamol is not authorized for the treatment of hsPDA. The dose regimen subjects in this group will receive is described considering the regimen used in the study of *Oncel et al*. in 2013.

IV ibuprofen is authorized for the treatment of hsPDA in preterm infants and the dose regimen is in accordance with the current prescribing information.

# 4 HYPOTHESIS AND OBJECTIVES

## 4.1 Hypothesis

1) Intravenous paracetamol is at least as effective as intravenous ibuprofen in the closure of hsPDA in LBW infants.
2) Intravenous paracetamol is safer than intravenous ibuprofen in the closure of hsPDA LBW infants.

## 4.2 Objectives

1) Test the effectiveness of intravenous paracetamol in the treatment of hsPDA in LBW infants, comparing it with intravenous ibuprofen. Main efficacy endpoint will be rates of ductal closure of both drugs after first course of treatment.
2) Evaluate the safety of intravenous paracetamol, used for the treatment of hsPDA in LBW infants, comparing it with intravenous ibuprofen. Safety endpoint will be the rate of side effects of both drugs.

## 5 STUDY DESIGN

This is a multicenter, prospective, single blinded, randomized, controlled, parallel-group and non-inferiority clinical trial designed to evaluate the efficacy and safety of IV paracetamol versus IV ibuprofen for the treatment of hsPDA in LBW infants. The study will be conducted in the neonatal intensive care units of Hospital Universitari Josep Trueta (HUJT), Girona and Hospital Universitari Vall d´Hebron (HUVH), Barcelona. HUJT will be the reference center

Subjects will be randomized in a 1:1 ratio to IV ibuprofen or IV paracetamol.

### 5.1 Termination standard

The clinical trial will stop before the end if there is a justified request by the investigator or the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) because of any the following situations, determined in the paragraph 5 of article 65 of “Ley del Medicamento”: violation of the law, alteration of the conditions of authorization, failure to comply with the ethical principles in the RD 223/2004, or with the purpose to protect the rights and interests of subjects. The autonomous community on its own initiative or at the request of the hospital Ethical Committee can suspend the study if any of the aforementioned situations happens.

## 6 STUDY POPULATION

This is a multicentrical study, the sample will be extracted from the NICU of HUJT and HUVH.

### 6.1 Inclusion criteria

Subjects must meet all the following criteria prior to randomization:

- LBW (≤ 1500 g and > 500)
- Echocardiographic evidence of hsPDA (any one of the follow): a left atrium to aortic root diameter ratio of ≥1.4 in the parasternal long-axis view; a DA diameter of ≥1.4 mm/kg body weight; left ventricular enlargement; holodiastolic flow reversal in the descending aorta.

### 6.2 Exclusion criteria

Patients meeting any single exclusion criteria prior to randomization will be excluded from the study:

- Congenital heart disease which requires PDA to maintain blood flow
- Life-threatening infection
- Recent (within the previous 24 h) IVH grade 3–4
- Urine output <1 ml per kg per h during the preceding 8 h
- Serum creatinine concentration of 1.6 mg/dL or higher
- Platelet count < 60000/$mm^3$ µL or less
- Hyperbilirubinemia requiring exchange transfusion
- Active NEC or intestinal perforation
- Liver dysfunction.

### 6.3 Sample size

A study group of 67 patients is needed to detect a difference of at least 20% in the closure rate between the IV paracetamol and IV ibuprofen groups, assuming a closure rate of 80% with

intravenous ibuprofen, with a 95% confidence interval and a power of 80%, and anticipating a loss rate of 5% due to various causes during the study. Thirty four patients will be included in each group of treatment (randomization 1:1).

### 6.4 Screening and diagnose protocol for hsPDA

All preterm infants ≤ 27 weeks (gestational age) will be screened by echo. In patients > 27 weeks, an echo will be done only if they present suggestive signs and symptoms, or if they need respiratory support with CPAP (continuous positive airway pressure) or mechanical ventilation with a FiO2 >25%. If no PDA is diagnosed, echo only will be done if clinics appear.

Annex 1: Screening and diagnose protocol for PDA.

### 6.5 Estimated time of recruitment

We need to treat 68 patients. About 20 patients with the needed characteristics (LBW infants with hsPDA) are admitted in HUJT every year, and 30 in HUVH, considering that about a 10% of the candidate patients may not want to participate (parents or legal tutors don´t want subjects to participate), we estimate that it will last around 24 months to treat 68 patients.

The study will start on January 1, 2015, the end of the study will occur when the last patient enrolled has been discharged, approximately on December 31, 2016.

## 7 ENRROLLEMENT AND RANDOMIZATION PROCEDURES

All LBW infants, with diagnosed hsPDA admitted in the NICU of the aforementioned hospitals will be assessed to participate in the study. After it has been verified that they are eligible per inclusion and exclusion criteria, they will be enrolled in the study once parents or legal tutors have signed the informed consent.

The randomization process will be conducted by the main investigator by simple randomization. Enrolled participants will be randomly assigned at a 1:1 ratio between IV paracetamol and IV ibuprofen groups by using cards in sequentially numbered, sealed opaque envelopes. Each patient will be assigned an identification number

Subjects withdrawn from the study will not be replaced.

A pediatric cardiologist will perform efficacy evaluation, and this person will be blinded to the treatment group; also will be blinded to the treatment group the neonatologist who will determine the presence of adverse events and the main investigator. Separate study personnel will treat subjects (treating nurse) in order to protect against possible unblinding of treatment assignment.

Annex 2: Flow diagram.

# 8 STUDY TREATMENT

## 8.1 Study treatment groups

Infants will receive one of the following dose regimens:

1. Treatment group receives IV paracetamol at the doses of 15 mg/kg every 6 hours during 72 hours (12 doses), we will use a solution for perfusion with a concentration 10 mg/ml (Paracetamol Actavis®)

2. Control group receives IV ibuprofen, an initial dose of 10 mg/kg followed by 5 mg/kg at 24 and 48 hours, we will use a solution for perfusion with a concentration 10 mg/ml (Neoprofen®)

## 8.2 Treatment duration

After the first course of treatment, echo will determine if a second course of treatment is needed. If the ductus remains opened by the end of the first course of treatment, another course will be started, with the same medication regimen. If there is closure and reopening of the ductus, a second course of treatment will be started too. If only minor ductal shunting is present after two courses without the need of respiratory support, no further treatment will be given. If second course of treatment also fails, surgical closure is indicated.

Annex 3: Treatment diagram

## 8.3 Other treatments

For all patients, ventilator management, fluid therapy and other supportive care will be applied according to the usual practice of the center.

## 8.4 Practical considerations

Study treatment must be stored in a secure location and it must only be dispensed by a pharmacist or medically qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once treatment is dispensed to a subject, it can only be used by that subject.

Accurate records demonstrating dates and amount of study treatment received and dispensed, and accounts of any study treatment accidentally or deliberately destroyed must be registered. All used and unused vials and syringes must be saved for study treatment accountability.

### 8.5 Removal of subjects from treatment

The occurrence of any of the following conditions will prompt the stopping of treatment on the affected subject: renal failure, NEC, IVH grade 3-4, gastrointestinal bleeding. These subjects must permanently discontinue the study treatment, and they may be treated with alternative approved therapies according to local practices. They should leave the study, and they will not be replaced.

### 8.6 Withdrawal of subjects from the Study

Subjects must be withdrawn from the study for any one of the following reasons: parents or legal tutor retire the consent to participate in the study, parents are unwilling to comply de protocol, at the discretion of the investigator for medical reasons (safety, adverse events).
Subjects withdrawn from the study will not be replaced.

## 9 STUDY VARIABLES

In every subject enrolled in the study, we will collect the following baseline characteristics:

Clinical characteristics: gestational age (weeks), gender (male or female), birth weight(g), cesarean birth (yes or not), pregnancy induced hypertension (PIH) (yes or no), antenatal glucocorticoid (yes or no), perinatal asphyxia (yes or no), early-onset infection (yes or no), surfactant treatment (yes or no), nasal continuous airway pressure (NCPAP) (yes or no), Nasal Synchronized Intermittent Mandatory Ventilation (NSIMV) (yes or no*),* Synchronized Intermittent Mandatory Ventilation (SIMV) (yes or no), IVH grade 1-2 (yes or no).

Echocardiographic characteristics: ductal diameter (mm), LA/Ao ratio.

PIH is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in a previously normotensive pregnant woman who is ≥20 weeks of gestation and has no proteinuria or new signs of end-organ dysfunction.

Perinatal asphyxia is defined as the presence of the following criteria: evidence of intrapartum metabolic acidosis ((pH < 7,00 and base deficit **≥** 12 mmol/L), acute encephalopathy in the first hours of life and cerebral palsy, spastic quadriplegia or dyskinetic cerebral palsy.

Early-onset infection defined as an infection acquired before 72 hours of life.

IVH grades are defined by the scale of *Papile et al.*

Annex 4.1: Baseline data collection sheet.

# 10 ENDPOINTS AND ASSESSMENTS

## 10.1 Efficacy of the treatment

Main endpoint will be the rates of ductal closure of both drugs after the first course of treatment. During the treatment, daily echo will be performed to assess the efficacy of IV paracetamol versus IV ibuprofen.

Other efficacy endpoints will be ductal closure rate after the second course of treatment in patients whose duct failed to close after the first course, overall closure rate, reopening after closure, reclosing rate (ductal closure after continuing drug treatment among infants with ductal reopening) and mean hours needed for closure in each group. Ductal closure will be documented as the absence of ductal blood flow on the color Doppler echocardiography after the first course of treatment.

Echocardiographical results of each patient will be documented in an individual data collection shit (Annex 4.2: Echocardiographical data collection sheet).

## 10.2 Safety of the treatment

Safety endpoints will be the presence of adverse events associated with the study treatments in each group of treatment, including early adverse events (oliguria, renal failure, NEC, gastrointestinal bleeding, IVH grade 1-2, IVH grade 3-4, hyperbilirubinemia and death) and late adverse events (BPD, PVL, NEC, sepsis and death). Early adverse events are defined as those occurring during and up to 1 week after administration of the treatment, and late adverse events are those occurring until the moment of discharge.

24 hours urine output will be collected daily during the treatment. Oliguria is defined as a urine output of 1 mL/kg/h or less during a 24 hour collection period. Renal function will be evaluated also by serum creatinine concentrations, and renal failure is defined as a decrease in diuresis down 1ml/kg/h. or an increasing of Cr up 1.8 mg/dl.

Bilirubin levels will be assessed daily during the treatment, and hyperbilirubinemia is defined as a value of serum bilirubin for which the child needs exchange transfusion according to actual nomograms of the American Academy of pediatrics.

NEC will be diagnosed when the clinical signs and radiographic evidence of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air is present.

Gastrointestinal bleeding is tendency to bleed as revealed by hematuria, blood in the endotracheal or gastric aspirate or stolls, or oozing from puncture sites.

Cranial ultrasound examination will be performed before and after treatment for the assessment of IVH or PVL.

BPD is defined as the need for supplemental oxygen after 28 days of life, in association with typical radiographic findings.

All tests will be performed and processed according to the usual practice of the hospital. A neonatologist is will diagnose possible adverse events.

Any adverse event, even those non-described as safety endpoints, will be documented in a personal data collection sheet. (Annex 4.3: Safety data collection sheet)

## 11 EXECUTION PLAN AND SCHEDULE OF EVENTS

Firs, this protocol needs the approval by the hospital Ethics Committee and obtain authorization form the AEMPS.

Each subject participating in the study will pass through the following phases:

1. Selection of subjects to be included in the study (according to inclusion and exclusion criteria). The investigator will determine if a subject is eligible for the study or not.
2. Parents or legal tutors must sign the informed consent.
3. Enrollment in the study, randomization, assignation to an identification number and allocation in one of the intervention groups
4. Collection of baseline data from clinical records. Patients will be done an echocardiography to determine baseline echocardiographic data, and a cranial ultrasound to diagnose possible IVH or PVL.
5. Start of the first course of the assigned treatment.
6. Efficacy and safety assessments: daily echo from the start of the first course of treatment, daily renal function and bilirubin assessments, cranial ultrasound after treatment. Remain alert to the presence of any adverse event. During and up to 1 week after administration of the drug early adverse events will be documented. Late adverse events will be documented until the moment of discharge.
7. Analysis of results.

If a second course of treatment is needed, the same efficacy and safety assessments than in the first course will be done during it.

While participating in the study patients will be monitored according to standard clinical practice.

After the trial ended results must be sent to the AEMPS. The investigator, with his signature, is responsible of the accuracy of the data reflected in the communication to the AEMPS. The ending of the study will also be reported to the local Ethical Committee and to the autonomous community.

The study will finish when the last treated patient is discharged.

Annex 5: Schedule

### 11.1 Tasks and research team

In each of the involved centers (HUJT and HVH) we will assign a principal investigator, and three co-investigators: a pediatric cardiologist, a neonatologist and a nurse. The pediatric cardiologist and the neonatologist will be blinded to the treatment groups.
We will hire an intern to handle data collection and entering data into the database.

The nurse will treat the subjects. During the treatment renal function tests and bilirubin levels assessments will be performed according to the usual clinical practice.

The pediatric cardiologist will assess the efficacy of both drugs. The nenonatologist will perform a cranial ultrasonography before and after treatment, and diagnose the occurrence of adverse events.

It is imperative that subject treatment assignments and any information such as laboratory results that may reveal the identity of the assigned treatment are not shared with the pediatric cardiologist and the neonatologist.

The statistical analysis will be performed by the main investigators.

## 12 ADVERSE EVENTS

An adverse event (AE) is considered any undesirable experience occurring to a subject during the clinical trial, whether or not considered related to the investigational product

Serious AE is any AE that results one of the following: death, imminent threat to life, permanent or severe disability or any adverse events that the investigator considered important for any reason.

Unexpected AE is any non-described experience related with the treatment drugs.

During the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

A record of AE and severe AE occurring during the clinical trial from the time of the sign of the informed consent must be kept. Any AE will be collected in the safety data collection sheet.

Any important information related with the safety of the study treatments (unexpected and severe AE) will be notified to the AEMPS, to the autonomous community and to the hospital Ethical Committee.

## 13 STATISTICAL ANALYSIS

Data will be introduced in the database (Access 2013) according to the project progresses. SPSS software (version 20.0) will be used for all statistical analyses.

GA and BW values will be given as the mean ± SD. Gender values will be given as number of males in percentage. Ductal diameter and LA/Ao values will be given as the mean ± SD. All other variables will be given in percentages.

Efficacy endpoints will be given as percentages in each group of treatment, except mean hours needed for closure, which will be as mean ± SD.

The presence of early or late AE will be given as percentages in each group of treatment.

Interim analyses will be performed for main and secondary outcomes at 50% recruitment.

The study will be terminated if a difference of 20% in the main outcome is found.

Continuous data will be given as means $\pm$ SD. Differences of means between groups will be determined by the t test for parametric continuous data, and Wilcoxon rank-sum test for non-parametric continuous data.

Qualitative variables will be defined with percentages. Differences of percentages between groups will be determined by the chi square for parametric categorical data, and Fisher exact test for non-parametric categorical data.

A multivariate analysis model will be performed with a logistic regression in with de independent variable will be the closure ductus percentage and the dependent variables will be the received drug, birth weight, gestational age, maternal treatmen with corticoids and the present of early onset infection.

Non-inferiority analysis is a statistical method that is used to determine whether a new drug is non-inferior to a drug of known efficacy. A new drug is considered at least as effective as the known drug if $P<0.05$ or $C_L>-\delta$ ($C_L$ is the lower limit of the 95% CI of the difference between two groups; $\delta$ is the non-inferiority margin).

## 14 OPPORTUNITIES AND LIMITATIONS OF THE STUDY

The number of patients required for the study can be ensured in a reasonable period of time at the departments of neonatology of HUJT and HUVH. This is a multicenter study, so we can generalize conclusions. Staff in the research group is experienced in conducting clinical trials.

This study us the first clinical trial in the literature using IV paracetamol treatment for PDA. If paracetamol is indeed proven to be effective, it could become the treatment of choice for the management of PDA, mainly due to its more favorable side effect profile.

**Means available:**

The project will be held on 2 centers with the necessary means to conduct assessments for the study (for diagnose of PDA and efficacy assessments the two centers have echocardiography devices; for baseline and safety assessments centers have clinical laboratory, and each center will take care of the cost of the analysis). We also have necessary computer equipment and programs.

## 15 ETHICAL ASPECTS

This protocol must obtain the approval from the Ethics Committee of the HUJT (reference committee) and from the AEMPS.

The trial will be performed in conditions of respect for the fundamental rights of the person and for ethical postulates affecting biomedical research involving human subjects, the contents being followed in the declaration of Helsinki (Seul 2008) (Annex 6)

Parents or legal tutors of elegible subjects must sign an informed consent before enrollement. Originally granted consent may be revoked. Parents will be given an information sheet. (Annex 7)

The current legislation about personal data confidentiality will be respected, as well as the ethical standards about clinical trials in pediatric patients.

## 16 STUDY REQUIREMENTS

**Human resources**

- Hire an intern for collecting baseline data and introduce data in the database. This intern will work part time and he will divide his job between the two involved hospitals. 400 €/month (24 months): **9600 €**
- No funding required for pediatric cardiologists, neonatologists or nurses involved in the study.

**Material resources**

- Paracetamol: 34 patients will be treated with paracetamol. We will use paracetamol at a concentration of 10 mg/ml. Each course of treatment is a total of about 180 mg of paracetamol (depending on the subject weight). Assuming that about 10 patients may need a second course of treatment (a total of about 360 mg), we need a total of about 800 ml of paracetamol solution for perfusion (concentration of 10mg/ml): **15 €**
- No funding required for ibuprofen treatment, because it is the drug used as first line treatment in usual clinical practice.
- No funding required for echocardiography devices, fungible materials or laboratory tests.

**Others**

- Liability insurance: **4000 €**
- Congresses and conferences: **1500 €**
- Subsistence and coordination meetings between the centers: **300 €**
- Publication of results: **2500 €**

Total others: **8300 €**

**Overhead (20% of the total): 3583 €**

**Total: 21498 €**

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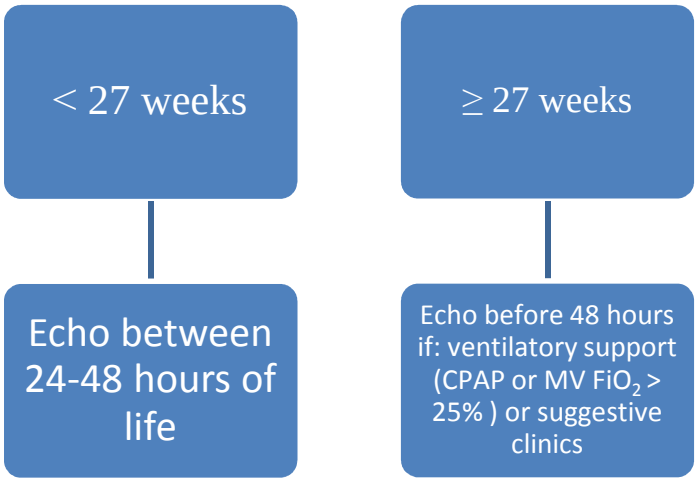
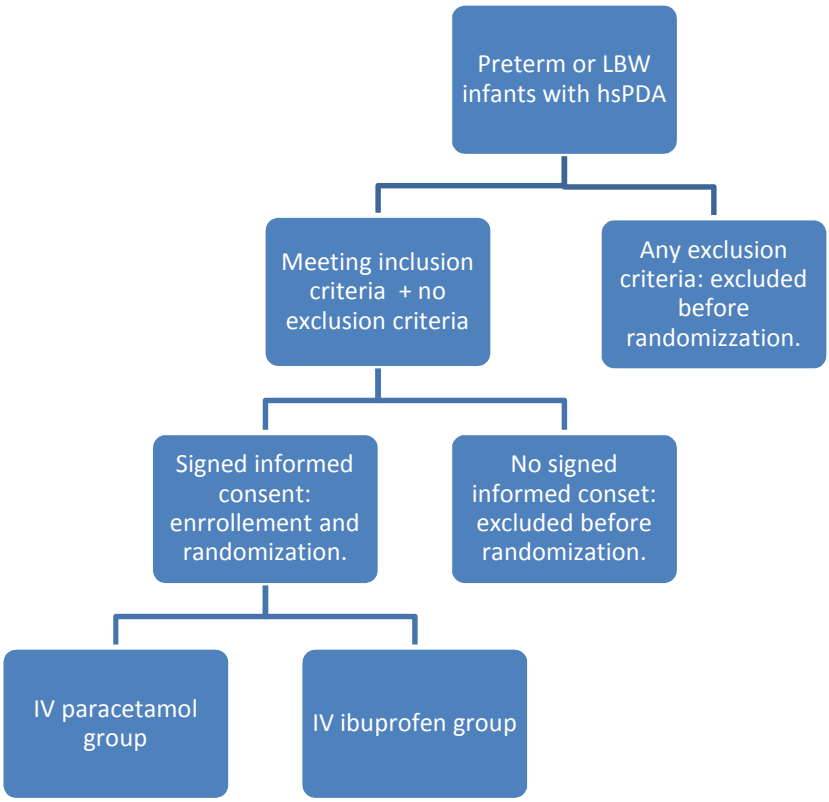
# 18 ANNEXES

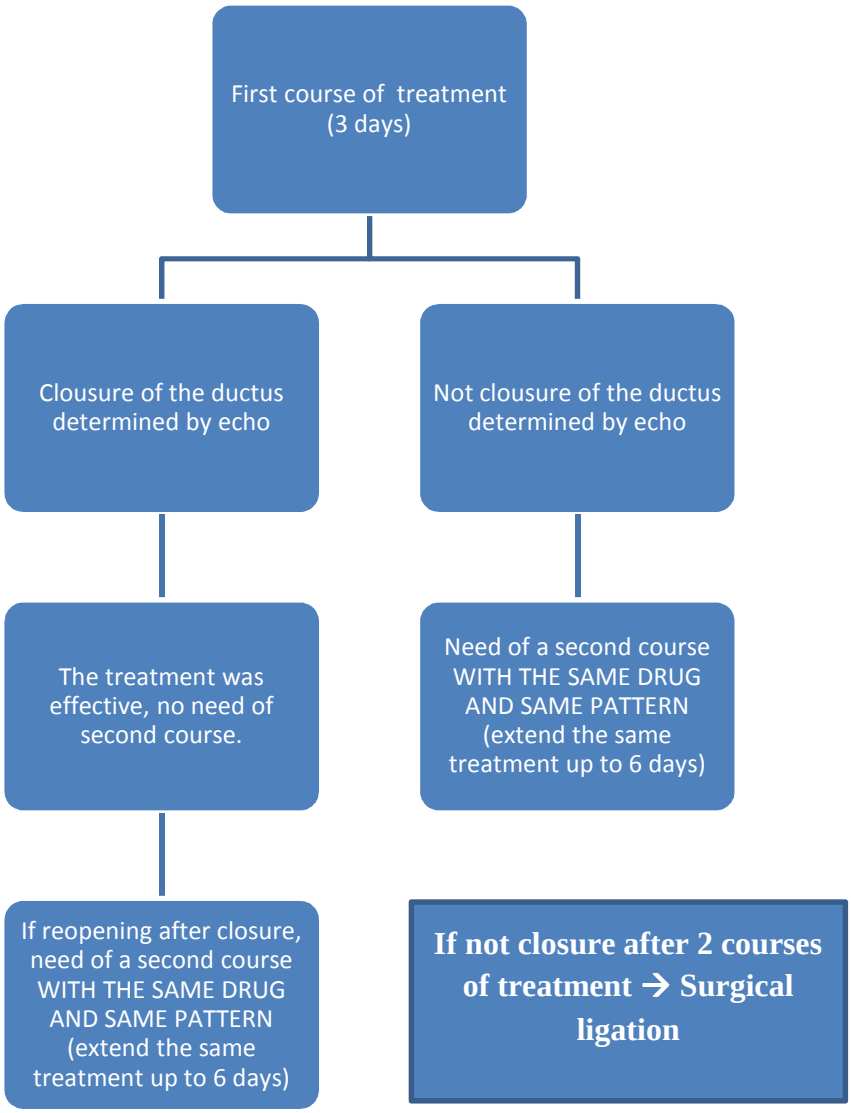
## 18.1 ANNEX 1: SCREENING AND DIAGNOSE PROTOCOLFOR PDA



## 18.2 ANNEX 2: FLOW DIAGRAM



## 18.3 ANNEX 3: TREATMENT DIAGRAM



## 18.4 ANNEX 4: DATA RECOLLECTION SHEETS

### 18.4.1 BASELINE DATA

| **Date and time:**<br>**Patient number:**<br>**Person collecting the data:** |
|---|
| **Gestational age (weeks)** |
| **Gender (male or female)** |
| **Birth weight (g)** |
| **Cesarean birth (yes or no)** |
| **PIH (yes or no)** |
| **Antenatal corticoid (yes or no)** |
| **Perinatal asphyxia (yes or no)** |
| **Early onset infection (yes or no)** |
| **Surfactant treatment (yes or no)** |
| **NCPAP (yes or no)** |
| **NSIMV (yes or no)** |
| **SIMV (yes or no)** |
| **IVH grade 1-2 (yes or no)** |
| **Ductal dm (mm)** |
| **La/Ao ratio** |
| **Days of life at baseline (days)** |

### 18.4.2 ECHOCARDIOGRAHPY DATA

| **Date and time:**<br>**Patient number:**<br>**Person collecting data:** | |
|---|---|
| **Primary closure** | Yes/no |
| **Secondary closure** | Yes/no |
| **Reopening after closure** | Yes/no |
| **Reclosure** | Yes/no |
| **Hours needed for closure** | |

### 18.4.3 SAFETY DATA

| | |
|---|---|
| **Date and time:**<br>**Patient number:**<br>**Person collecting data:** | |
| **EARLY AE** | |
| **Oliguria** | Yes/no |
| **Renal failure** | Yes/no |
| **NEC** | Yes/no |
| **IVH 1-2** | Yes/no |
| **IVH 3-4** | Yes/no |
| **Hyperbilirubinemia** | Yes/no |
| **GI bleeding** | Yes/no |
| **LATE AE** | |
| **BPD** | Yes/no |
| **PVL** | Yes/no |
| **NEC** | Yes/no |
| **ROP** | Yes/no |
| **Sepsis** | Yes/no |
| **Death** | Yes/no |
| **OTHER AE** | |
| | |

### 18.5 ANEX 5: SCHEDULE

| Tests and assessments | Diagnose of hsPDA | Start of the first course of treatment (Day 1) | Day 2 of treatment | End of the first course of treatment (Day 3) | Follow up until discharge |
|---|---|---|---|---|---|
| **Informed consent** | X | | | | |
| **Collection of baseline data from medical history** | X | | X | | |
| **Randomization and treatment assignment** | | X | | | |
| **Daily echocardiography** | X | | | | |
| **Cranial ultrasound** | X | | | X | |
| **Study drug administration** | | X | | | |
| **Renal function assessments** | | X | | | |
| **Bilirubin levels** | | X | | | |
| **Adverse events** | | X | | | |
| **Analysis of results** | | | | | X |

If a second course of treatment is needed, the same assessments will be done than in the first course. During all the study process, patients will be monitored according to local clinical practice.

## 18.6 ANNEX 6: HELSINKI DECLARATION (SEUL 2008)

**WORLD MEDICAL ASSOCIATION 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

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

### A. INTRODUCTION

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 not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

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

4. 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 Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. 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 current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should 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.

**B. PRINCIPLES FOR ALL MEDICAL RESEARCH**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 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 change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

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

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

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

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, 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.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent 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.

29. 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 population. In such circumstances the physician should 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 should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

31. The physician may combine medical research with medical care only to the extent that the research 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.

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

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it,

for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or 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. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

## 18.7 ANNEX 7: INFORMATION SHEET FOR PARENTS AND INFORMED CONSENT

**INFORMACIÓ ALS PARES**

Estudio: Paracetamol intravenós versus ibuprofè intravenós per al tractament del ductus arteriós persistent en nens de baix pes al néixer: un assaig clínic controlat.

Ens dirigim a vostè per informar-lo sobre un projecte que s'està portant a terme en la unitat de neonatologia dels hospitals universitaris Josep Trueta en Girona i Vall d´Hebron en Barcelona, sobre el tractament del ductus arteriós persistent, al qual s'invita al seu fill/a ha participar. L'estudi ha estat ja revisat i aprovat pel comitè Ètic del Hospital Universitari Josep Trueta, hospital de referència de l'estudi.

La col·laboració que sol·licitem és la següent:

- Administració aleatòria d'un dels dos fàrmacs, paracetamol endovenós o ibuprofè endovenós. L'ibuprofè endovenós es el fàrmac que s'utilitza habitualment per a tractar el ductus persistent, és eficaç i no exempt d'efectes secundaris. El paracetamol es un fàrmac que ha set molt estudiat en els últims anys, mostrant fins el moment ser segur i eficaç.
- Obtenció d'informació corresponent a analítiques prèvies.

**Participació voluntària**

Abans de tot necessitem el seu consentiment lliure i voluntari. Volem proporcionar-li la informació correcta i suficient per a que pugui valorar si vol o no que el seu fill participi en l'estudi. Per tant, llegeixi aquesta fulla informativa amb atenció i nosaltres li aclarirem els dubtes que puguin sorgir.

La participació del seu fill en l'estudi es voluntària, pot decidir que no participi o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que per això s'alteri la relació amb el seu metge ni es produeixi cap perjudici en el seu tractament.

**Descripció de l'estudi**

El grup d'investigació que realitza aquest treball està especialitzat en nounats i complicacions relacionats amb la prematuritat. El ductus arteriós persistent és un defecte cardíac freqüent en recent nascuts prematurs o de baix pes, que necessiti tractament per a evitar les possibles i greus complicacions que puguin causar: respiratòries, neurològiques, gastrointestinals...

Els tractaments actuals per a tractar aquesta malaltia, són eficaços però tenen molts e importants efectes secundaris. Intentem buscar una nova opció, que sigui també eficaç però produint menys efectes secundaris. En aquest estudi investiguem sobre el paracetamol, un fàrmac que ha set molt estudiat en els últims anys, mostrant fins el moment ser segur i eficaç.

El seu fill serà assignat aleatòriament en un dels dos grups de tractament: tractament clàssic (ibuprofè) o nova opció terapèutica (paracetamol).

Les possibilitats d'aparició d'efectes adversos existeix amb els dos fàrmacs. En cas de que apareguin seran tractes com siguin necessaris, tenint sempre com a prioritat el benestar del pacient.

**Confidencialitat**

Les dades recollides seran confidencials, en cap cas el seu nom apareixerà en la publicació dels resultats.

La seva privacitat està protegida per les lleis nacionals (LO15/1999, LGC5/2002 i per la llei 14/2007 d'Investigació Biomèdica) i europea (95/46/CE).

D'acord amb la llei LO15/1999, vostè pot exercir el seu dret a l'accés, modificació, oposició i cancel·lació de les seves dades, i també pot sol·licitar la destrucció de les seves mostres.

**Compensació econòmica**

La donació i utilització de mostres biològiques humanes són gratuïtes. La seva participació en l'estudi no rebrà cap compensació econòmica.

En el cas de produir-se un desenvolupament comercial dels coneixements generats, els possibles beneficis seran per a cobrir costos científics. Firmant aquest consentiment vostè renúncia als drets sobre qualsevol ús comercial amb la informació o mostres que vostè està cedint.

**CONSENTIMENT INFORMAT**

Jo _____ , pare/mare/tutor de legal de _____ :

- He llegit la fulla informativa que se m'ha entregat
- He pogut fer les preguntes que he considerat sobre l'estudi
- He rebut suficient informació sobre l'estudi
- He parlat amb: (nom de l'investigador) _____ .
- Comprenc que la participació del meu fill és voluntària
- Comprenc que les mostres obtingudes seran etiquetades amb un codi per a mantenir la confidencialitat de les dades.
- Comprenc que puc rebutjar el meu consentiment en qualsevol moment, sense tenir que donar explicacions i sense que aquest fet alteri la meva assistència sanitària.

Firma del pare/mare o tutor legal:

Firma de l'investigador:

Data:

Data: