UdG
Facultat de Medicina

COMPARISON OF TWO WEANING PROTOCOLS IN EXREMELY AND VERY PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME

A RANDOMISED, MULTICENTRE CLINICAL TRIAL

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1. ABREVIATIONS

WHO – World health organization

NICU – Neonatal Intensive Care Unit

ABC – Airway, breathing, circulation

CPAP – Continuous Positive Airway Pressure

IVH – Intraventricular hemorrhage

GM – Germinal matrix

VEGF – Vascular endothelial growth factor

PHVD – Posthemorrhagic ventricular dilatation

GMH - Germinal matrix haemorrhage

GMH-IVH – Germinal matrix and intraventricular hemorrhage

US – Ultrasound

ROP – Retinopathy of prematurity

VPCs – Vascular Precursor Cells

PUFAs - Polyunsaturated fatty acids

NEC – Necrotizing enterocolitis

GI – Gastrointestinal

IgA – Immunoglobulin A

BPD – Bronchopulmonary dysplasia

LBWI – Low birth weight infants

IUGR – Intrauterine growth restriction

CT – Computed tomography

PH – Pulmonary hypertension

ECHO – Echocardiogram

GA – Gestational age

PMA – Postmenstrual age

GBS - Group B Strep

NICHD – Child Health and Human Development

NRDS – Neonatal respiratory distress syndrome

RDS – Respiratory distress syndrome

FRC – Functional residual capacity

H_2O – Water

FiO_2 – Fraction of inspired oxygen

SpO_2 – Blood oxygen saturation and pulse

ºC –Degree Celsius

LISA – Less invasive surfactant administration

RR – Respiratory rate

PEEP – Positive end-expiratory pressure

PIP – Peak inspiratory pressure

NIV – Non-invasive ventilation

V/Q – Ventilation perfusion

COPD – Chronic obstructive pulmonary disease

NP – Nasopharyngeal

NIPPV – Nasal intermittent positive pressure ventilation

BIPAP – Bilevel positive airway

ACVGV – Assist-control volume guarantee ventilation

ACV – Assist-control ventilation

PSV – Pressure support ventilation

HR – Hearth rate

$PETCO_2$ – End tidal CO_2

MV – Mechanical ventilation

HUJT – Hospital Universitari Doctor Josep Trueta

CPR – Cardiopulmonary resuscitation

RR – Respiratory rate

Sat Hb – Hemoglobin saturation

ID – Identification of patient

IQR – Interquartile range

WMA – World Medical Association

EU – European Union

CEIC – Comité d'Ètica i d'Investigació Clínica

MI – Main investigator

SC – Study coordinator

HC – Hospital coordinators

CI – Co-Investigators

HCP – Health care professionals

DM – Data manager

SS – Statistical specialist

2. ABSTRACT

BACKGROUND:

The most common complication of prematurity is the newborn respiratory distress syndrome. It is a pathology that mainly affects premature infants born before 32 weeks of gestation. About 40% of these neonates require invasive mechanical ventilation to manage the syndrome. Recently, it has been recognised that reducing intubation time and the number of reintubations is of great significance in reducing further complications. Therefore, one approach to decrease complications is to identify a weaning protocol that facilitates posterior extubation.

OBJECTIVE:

The main objective is to compare the number of reintubations of *pressure support ventilation* and *assist control volume guarantee ventilation***,** in extremely and very preterm neonates with newborn respiratory distress syndrome with invasive mechanical ventilation.

DESIGN:

This study is designed as a randomized, open label, multicentrical clinical trial. It will be conducted in 5 different hospitals of Catalonia.

PARTICIPANTS:

542 participants will be enrolled from 5 hospitals using a stratified consecutive sampling, and the time of recruitment will be approximately of 2 years and two months. These patients will be randomized in two groups, one for each weaning protocol, with a 1:1 ratio.

KEYWORDS:

Neonates, preterm, newborn respiratory distress syndrome (NRDS), invasive mechanical ventilation, pressure support ventilation (PSV), assist-control volume guarantee ventilation (ACVGV), weaning, extubation

3. INTRODUCTION

3.1 Prematurity

The World Health Organization (WHO) defines preterm birth as any birth occurring before 37 completed weeks of gestation since the first day of the mother's last menstrual period. Preterm birth can be further classified based on the gestational age:

- **Extremely preterm** (less than 28.0 weeks of gestation. 5% of preterm babies)
- **Very preterm** (between 28.0 and 31.6 weeks of gestation. 15% of preterm babies)
- **Moderate preterm** (between 32.0 and 33.6 weeks of gestation. 20% of preterm babies)
- **Late preterm** (between 34.0 and 36.6 weeks of gestation. 60% of preterm babies). (1)

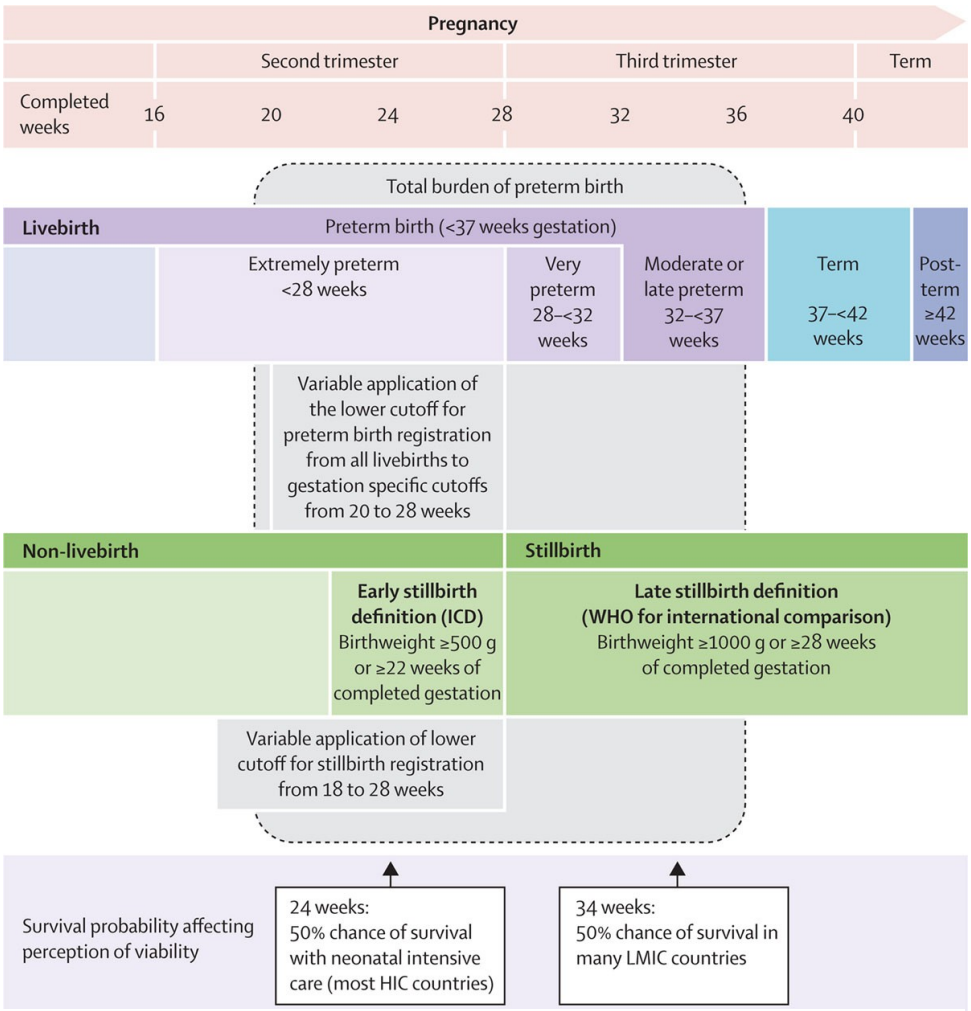


***Figure 1** - Overview of definitions for preterm birth and related pregnancy outcomes(2)*

HIC: High income countries
LMIC: Low or middle-income countries

3.1.1 Epidemiology of prematurity

Globally, approximately 385.000 neonates are delivered every day (2); in Spain, there were 329.892 births in 2022, with Catalonia recording 57.634 births.

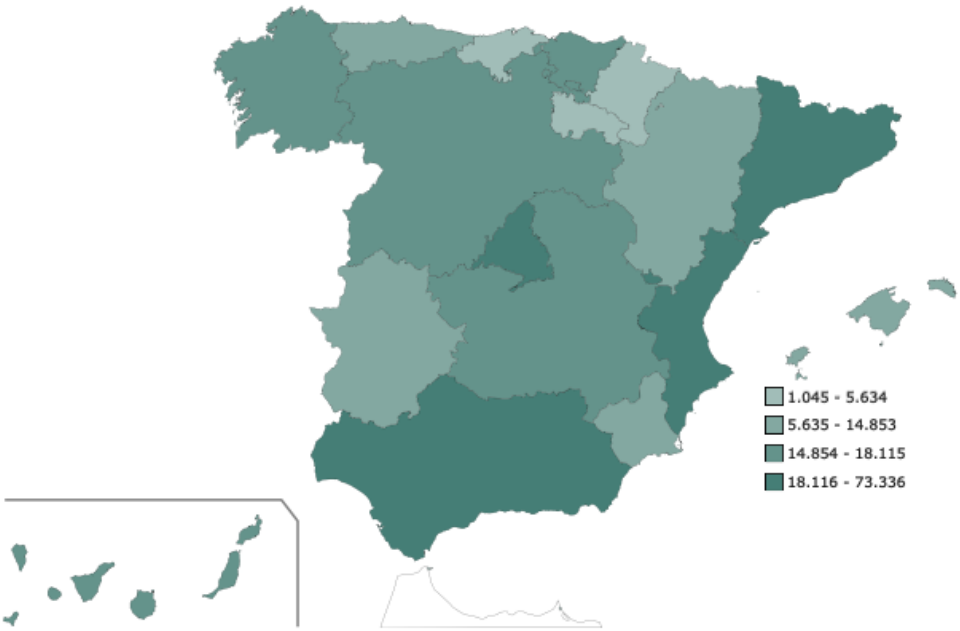


***Figure 2** - Number of births in each Autonomous Community in Spain, in 2022 (3)*

However, estimating the rate of preterm birth on a worldwide scale is challenging. In 2010, the estimated overall preterm birth rate was 11% of all deliveries (15 million neonates). (4)

In 2021, there were 20.455 preterm births in Spain, which accounted for approximately 7-8% of all newborns in the country.

According to the latest data from Catalonia, in 2021 there were 3.334 newborns that year. (5)

The rate of prematurity has increased compared to 50 years ago, although there has been a slight decrease in the last 20 years. (6)

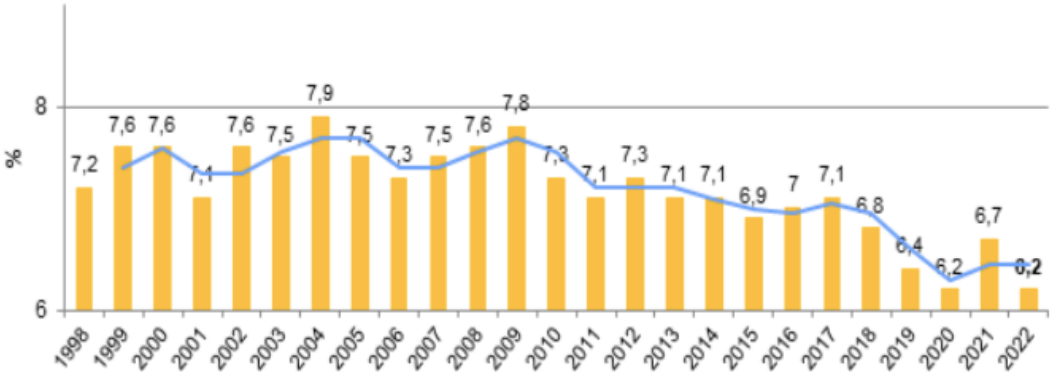


Figure 3 - Evolution of the percentage of babies according to prematurity at birth in Catalonia (6)

Premature babies can be classified into two major groups - those with threatened preterm labour and those with established preterm labour. Established preterm labour is a delivery induction or elective caesarean birth before 37 completed weeks of gestation for either maternal or foetal indications. (7) Understanding this classification is crucial to appreciate the recent surge in prematurity prevalence, which is largely attributed to the increase in established preterm labour cases.

3.1.2 Risk factors of preterm birth

All these factors increase the risk of having a preterm birth. They have been divided in the following categories:(8–11)

Obstetrics

- History of previous preterm birth
- History of second trimester miscarriage (> 16 weeks)
- Multiple pregnancy
- Vascular alterations
- Intraamniotic infection (chorioamnionitis)
- Premature rupture of membranes

Maternal

- Maternal age: there is an increased risk of prematurity in young mothers, especially those under 18 years of age (12) or over 35 years.
- Maternal size: There is an increased risk of prematurity if the maternal size is < 150 cm (13)
- Cervical surgery
- Congenital uterine anomaly
- Cervical dilation, uterine curettage
- Diabetes or gestational diabetes
- Sexually transmitted infection

Sociodemographic

- Smoking
- Consuming alcohol or other toxics
- Short intragestational period (period between delivery and conception of next gestation < 18 months, according to WHO definition)
- African-American and Afro-Caribbean race
- Maternal stress

Others

- Extrauterine infections

3.1.3 Neonatal assessment

One of the most important steps in the case of threatened or established preterm labour is to transfer the patient to a **level III centre** with access to a neonatal intensive care unit (NICU). This ensures the presence of a neonatologist during birth, enabling the newborn baby to receive immediate care, if required.(14)

There is a scoring system called the **Apgar score** (see Annex 1) that offers a standardized assessment for infants after birth. This method is a prompt way of evaluating the clinical condition of a newborn. The Apgar score consists of five components: colour, heart rate, reflexes, muscle tone, and respiration. A score of

0, 1, or 2 is assigned to each of these components. The Apgar score is recorded at 1 and 5 minutes after birth for all infants, and at 5-minute intervals (up to 20 minutes) for infants with a score less than 7. Consequently, the Apgar score quantifies clinical signs of neonatal depression, such as cyanosis, pallor, bradycardia, depressed reflex response to stimulation, hypotonia, and apnea or gasping respirations. It is a useful means of conveying information about the newborn's overall condition and response to resuscitation. However, resuscitation should be initiated before the 1-minute score is obtained, so it is not used to determine the need for initial resuscitation.(15,16)

3.1.4 Neonatal resuscitation

There is *The European Resuscitation Council Guidelines* from 2021, which indicates the steps to follow in case the newborn requires neonatal resuscitation (see Figure 4).

Neonatal resuscitation begins with the ABC approach: airway, breathing, and circulation.

Proper head positioning and ventilation with a mask and bag are essential to manage airway. CPAP (Continuous Positive Airway Pressure) is the preferred ventilation method as it assists in stabilising the functional residual lung capacity. Although in severe cases, CPAP may be inadequate and require invasive mechanical ventilation to support the newborn. Both CPAP and invasive mechanical ventilation are discussed in more detail in sections 3.3.2 and 3.3.3.

In addition to the ABC approach, newborns often require **stimulation**, which can promote increases in respiration and cardiac function through activation of the sympathetic-adrenal system; **suction,** that is used to remove amniotic fluid from the nasopharynx and oropharynx; and **drying and heating**, that can reduce the demand for oxygen needed to maintain temperature. (16)

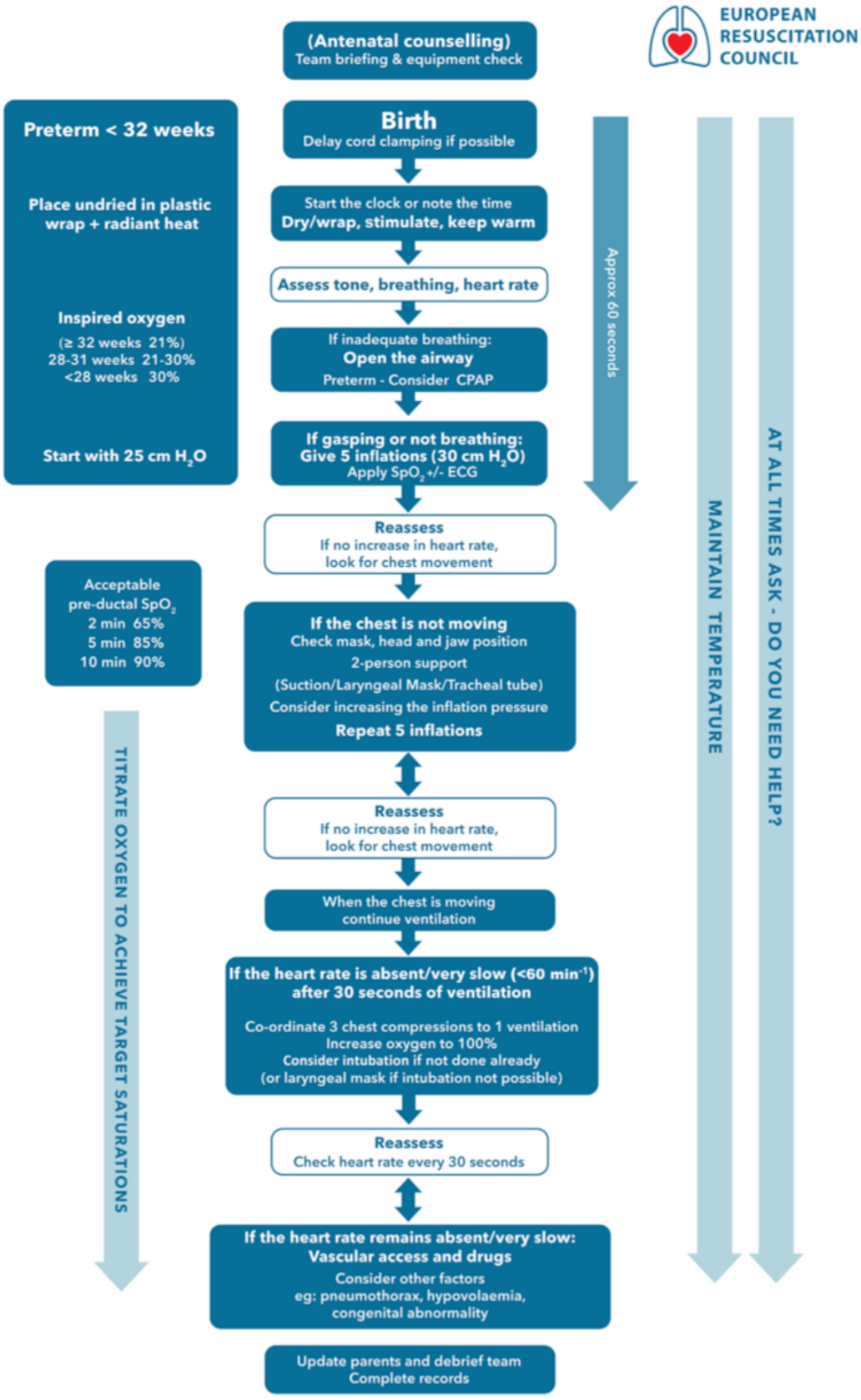


Figure 4 *- Newborn life support algorithm (17)*

3.1.5 Complications of preterm birth

The neonatal period is considered to be the first 4 weeks of life. The main factors responsible for mortality during this period are infections, preterm birth complications, and intrapartum-related neonatal deaths, also referred to as birth asphyxia. Globally, these three causes account for more than 80% of all neonatal deaths.

In recent years, the incidence of neonatal deaths resulting from infections has significantly declined. However, little progress has been made in reducing global mortality rates from preterm birth and intrapartum-related neonatal deaths (18,19)

Preterm birth is a significant cause of neonatal death and also causes many long-term problems in survivors. The risk of adverse outcomes decreases with increasing gestational age. (20)

Some of the common complications associated with premature birth are presented briefly below.

Intraventricular haemorrhage (IVH)

IVH is a major complication of prematurity. Its **pathophysiology** is multifactorial and complex. IVH typically initiates in the germinal matrix (GM), which is a richly vascularized collection of neuroglial precursor cells in the developing brain. The GM is initially the site where neuroblasts and glioblasts mitotic activity occurs before cells migrate to other parts of the brain. When cell division and migration are complete, the GM progressively decreases in size, with regression being almost complete by term equivalent age. So, it is a transient structure.

The microvasculature of the germinal matrix is fragile due to an abundance of angiogenic blood vessels that exhibit a shortage of pericytes, immaturity of basal lamina, and poor support from muscles or collagen. There is also a rapid angiogenesis due to high levels of VEGF (vascular endothelial growth factor) and angioprotein-2. The elevation of these growth factors may be attributed to a relative hypoxia of the germinal matrix perhaps resulting from high metabolic activity and oxygen consumption of the neural progenitor cells. (21–23)

All these factors, contribute to the high risk of this structure causing an intraventricular haemorrhage.

If the IVH is large, it can often be **complicated** by post-haemorrhagic ventricular dilatation (PHVD) or parenchymal haemorrhagic infarction and is associated with an increased risk of adverse neurologic sequelae. (21)

The **incidence** of GMH (germinal matrix haemorrhage) is directly related to the maturity, reflected by gestational age and birth weight of the infant. Nearly all cases of haemorrhaging take place within the first week of birth, with most occurring within 24-48 hours.

It is usually **diagnosed** during routine bedside US (ultrasound). Systematically performing US on admission and sequentially during the first week, allows for the most precise timing and identification of the haemorrhage. (21)

Classification:

Ultrasound description of GMH-IVH

Description	Generic term
Grade I: Germinal matrix hemorrhage	GMH
Grade II: Intraventricular hemorrhage without ventricular dilatation	GMH-IVH
Grade III: Intraventricular hemorrhage with acute ventricular dilatation (clot fills >50% of the ventricle)	GMH-IVH and ventriculomegaly
Intraparenchymal lesion—describe size, location	IPL or periventricular hemorrhagic infarction (PVHI) or venous infarction

Adapted from Volpe JJ (Ed) (2018). Volpe's neurology of the newborn, sixth edn, Elsevier, Philadelphia.

Figure 5 *- Classification of IVH depending on US description (21)*

There is **no specific therapy** to limit the extent of GMH-IVH once it has occurred. Therefore, current management of GMH-IVH is supportive and aimed at maintaining cerebral perfusion, minimising further brain injury and early recognition of complications. **General supportive measures** include prompt and adequate resuscitation and maintenance of arterial perfusion to avoid hypotension or hypertension and to preserve cerebral blood flow without significant impairment; adequate oxygenation and ventilation with specific avoidance of hypocarbia, hypercarbia and acidosis; and provision of appropriate fluid, metabolic and nutritional support. (23)

Retinopathy of prematurity (ROP)

ROP is a **multifactorial pathology** of retinal development, particularly of the retinal vascular network.

Retinal vascular development in utero is essentially in a state of physiological hypoxia. Two distinct phases of normal retinal vascular development have been described. The first phase is **vasculogenesis**, which lasts from 14 weeks to 21 weeks of gestation. During this phase, vascular precursor cells (VPCs) of mesenchymal origin arise from the optic nerve and form the four major arcades of the posterior retina. In the second phase, called **angiogenesis**, proliferating endothelial cells arise from the blood vessels formed in the first phase to form the capillary network. The nasal retina becomes vascularised by 8 months of gestation and the temporal retina shortly after term (around 40 weeks of gestation). A preterm infant at birth would therefore have an incompletely vascularised peripheral retina to varying degrees.

After birth, the physiological in-utero hypoxia is reduced and the newborn is now exposed to a state of hyperoxia (both due to atmospheric oxygen and supplemental oxygen).

In prematurity, retinal vascularisation is incomplete at birth, leaving avascular areas to form the basis of ROP. ROP develops in two phases. The first is called the **ischaemic phase**, in which hyperoxia contributes to the arrest of the progression of the retinal capillary bed associated with the degeneration of existing vessels - it can cause vaso-obliteration. The second, called the **proliferative phase**, is manifested by the proliferation of new vessels from areas of avascular ischaemia. However, this proliferation is anarchic and inefficient because the retina remains devoid of nourishing vessels. The growth of pathological new vessels is under the control of pro-angiogenic factors, including VEGF.

ROP is a leading cause of preventable blindness in children. Its **incidence** is increasing with the increasing survival of extremely premature babies.

The degree of prematurity is the most consistent **risk factor** for ROP. The lower the birth weight and the gestational age the higher is the risk for ROP. Several other postnatal factors may contribute to the development of ROP. These include, the use of supplemental oxygen, intraventricular haemorrhage, apnoea, mechanical ventilation, sepsis, surfactant therapy and anaemia.

Preventive strategies should be synergistic and complementary, including tight control of oxygen therapy, optimised nutritional intake and postnatal growth, breastfeeding, adequate supply of omega-3 PUFAs and control of hyperglycaemic episodes associated with prematurity. ROP requires a multidisciplinary management, including systematic screening, appropriate treatment, and long-term follow-up.

Current **screening** modalities are based on wide-field digital retinal imaging systems. The gold standard **treatment** for ROP remains laser photocoagulation.(24–26)

Necrotising enterocolitis (NEC)

Necrotising enterocolitis (NEC) is the leading cause of gastrointestinal death in preterm neonates, affecting 5-12% of neonates born at very low birth weight. (27)

Immature motility, digestion, absorption, immune defences, barrier function and circulatory regulation probably predispose the preterm infant to an increased risk of intestinal injury. Specifically, preterm neonates lack several GI defence mechanisms such as gastric acid, digestive enzymes, mucus production, peristalsis and polymeric immunoglobulin A (IgA). (28,29)

The **pathophysiology** of NEC is generally considered to be **multifactorial**, with common **risk factors** including low gestational age at birth, low birth weight, chorioamnionitis, mechanical ventilation,(30,31) genetic predisposition, intestinal immaturity and altered microvascular tone. This, together with a high likelihood of abnormal microbial colonisation in the intestine and a highly immunoreactive intestinal mucosa, leads to a confluence of predisposing factors. (28)

The excessive inflammatory process initiated in the highly immunoreactive intestine in necrotizing enterocolitis extends the effects of the disease systemically, affecting distant organs such as the brain and placing affected infants at significantly increased risk of neurodevelopmental delay. In fact, an infant recovering from necrotizing enterocolitis may have nearly a 25% chance of microcephaly and severe neurodevelopmental delays go beyond gastrointestinal concerns. (28,29)

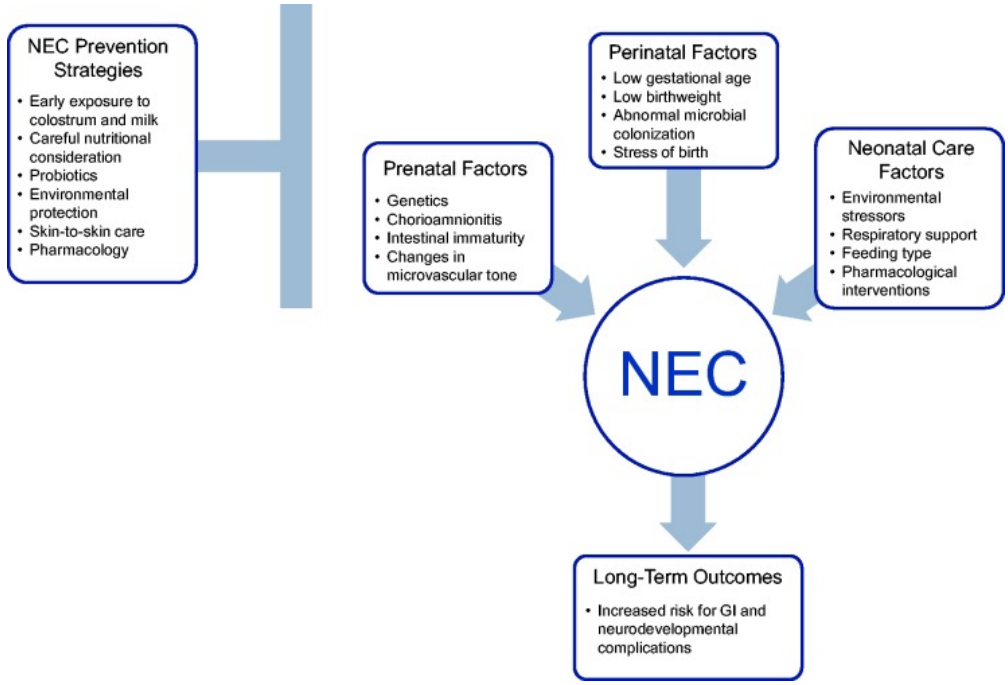


Figure 6 *- NEC risk, prevention, and outcomes (29)*

Some **preventive measures** for NEC and their levels of evidence, are described in Table 1.

Measures to Prevent Necrotizing Enterocolitis.*

Evidence of Efficacy and Safety	Evidence of Efficacy but Questionable Safety	Evidence of Efficacy in Animal Models but Not in Humans	Proposed Efficacy but Lacking Evidence
Breast-milk feeding	Enteral aminoglycosides	Anticytokines	Prebiotics (derived from plants and breast milk)
Nonaggressive enteral feeding	Probiotics	Growth factors	Microbial components and toll-like-receptor agonists
	Glucocorticoids		Glutamine, n-3 fatty acids
	Arginine		

Table 1 *- Preventive measures for NEC and their levels of evidence (28)*

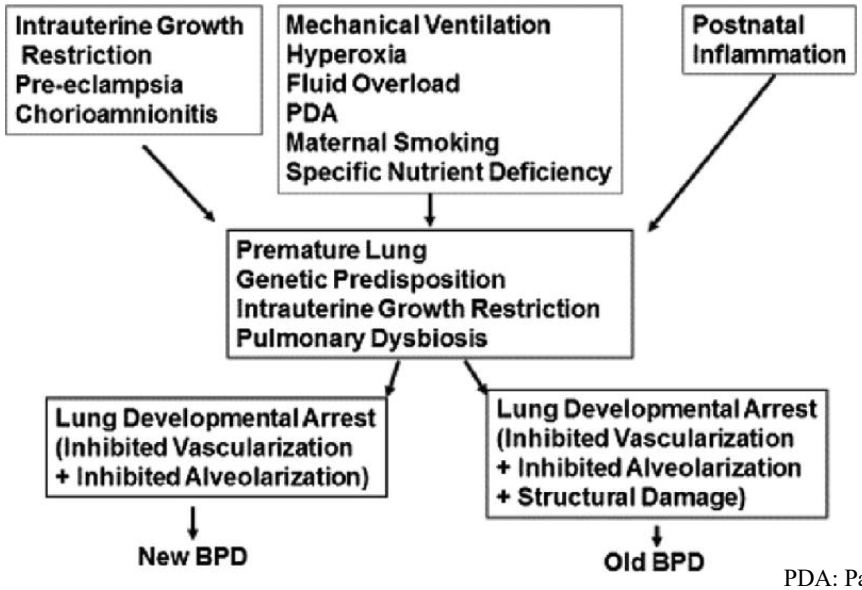
The **diagnosis**, **signs and symptoms** and **treatment** of NEC are summarised in Annex 2.

Bronchopulmonary dysplasia (BPD)

Bronchopulmonary dysplasia (BPD) is potentially one of the most devastating conditions in premature infants with longstanding consequences involving multiple organ systems including adverse effects on pulmonary function and neurodevelopmental outcomes.

BPD affects premature low birth weight infants (LBWI), is slightly more common in Caucasian males, and genetic heritability plays an important role in its pathogenesis.(32)

Premature birth truncates lung development and is often exacerbated by prenatal events such as intrauterine growth restriction (IUGR) and exposure to inflammation, and postnatal events related to initial resuscitation, oxygen administration, mechanical ventilation, and pulmonary and systemic infections, all of which can lead to arrested pulmonary vascular and alveolar development. It remains unclear whether prematurity itself causes BPD, or whether factors contributing to prematurity are the direct cause, or whether there are other as yet unrecognised factors that lead to BPD. (33) For example, in the presence of prenatal factors predisposing to BPD, mechanical ventilation and reactive oxygen species injury to the premature lung produces an exaggerated inflammatory response witn increases in proinflammatory cytokines, tumour necrosis factor and angiogenic factors, leading to aberrant tissue repair and arrest of lung development.(33)



PDA: Patent ductus arteriosus

***Figure 7** - Pathogenesis of BPD (33)*

The **clinical phenotype** of infants with BPD is highly variable. Depending on the severity of the disease they may or may not require respiratory support. Some may be tachypnoeic and, depending on the degree of pulmonary oedema, may have signs of respiratory distress such as retractions, rales, and increased work of breathing.

The **evaluation** of BPD includes a blood gas, a chest x-ray, and an assessment of the patient's nutritional status. Arterial blood gas may reveal hypoxia, hypercarbia, or acidosis. These patients remain on continuous pulse oximetry to achieve adequate oxygen saturation.

Chest radiographs may show decreased lung volumes, hyperinflation, areas of atelectasis, pulmonary oedema, and pulmonary interstitial emphysema. High-resolution CT (computed tomography) may show abnormalities not readily seen on routine chest radiographs. Infants with moderate or severe BPD should be screened for pulmonary hypertension (PH) by echocardiography (ECHO) at 36 weeks postmenstrual age (PMA).

The **diagnosis** of BPD is made clinically based on gestational age (GA), postmenstrual age, oxygen exposure and oxygen requirements at 36 weeks PMA. In 2001, the National Institute of Child Health and Human Development (NICHD) workshop proposed the current definition, in which infants born at less than or equal to 32 weeks GA with 28 days of oxygen exposure are diagnosed with mild, moderate, or severe BPD at 36 weeks PMA based on their respiratory support at that time.

The global aim in the **management** of infants with BPD is to support them during lung growth occurs, limit further lung injury, optimise lung function and detect complications associated with BPD.(34) Some measures include:

- Nutrition: they require an increased amount of energy, their nutritional requirements can be up to 140-150 Kcal/kg/day
- Fluid restriction: restriction to a total fluid volume of 120-150 ml/kg/day
- Minimise ventilator-associated lung injury: non-invasive ventilation is preferred if possible. If invasive ventilation is required, early extubation is recommended.

- The target saturation should be between 90 and 94%.
- Pharmacological interventions: possible use of systemic corticosteroids, diuretics, or bronchodilators

Sepsis

Neonatal sepsis is a systemic condition caused by bacteria, viruses, or fungi that results in haemodynamic changes and clinical symptoms, leading to significant morbidity and mortality.

When discussing sepsis in neonates, it is important to distinguish between two different types of sepsis, which have different epidemiology, aetiology, risk factors, and management.

Early-onset sepsis (vertical sepsis)

Early-onset sepsis can develop in utero as a result of either **transplacental** or, more commonly, **ascending bacterial** transmission from the vaginal environment after rupture of the membranes. In addition, the newborn can contract infection during passage through the **birth canal** as a result of exposure to potentially pathogenic microorganisms.(35)

The **diagnosis** of early-onset sepsis is confirmed when there are clinical signs (refer to Table 2) of sepsis within the **first 72 hours** of life, along with the identification of a pathogenic microorganism in a blood culture.(35,36)

In the last 20 years, **the incidence** of vertical sepsis in Spain has decreased due to the neonatal GBS (Group B Strep) prevention strategy. The most common **aetiologies** are GBS, E.coli, Enterococcus spp and Listeria monocytogenes. (36)

Mortality is 10% globally, reaching 30% in newborns weighing < 1.500 g. (36)

The **clinic** is summarised in the Table 2.

The main **risk factors** are (36):

- Maternal colonisation for GBS in absence of a correct intrapartum antibiotic prophylaxis.
- Spontaneous preterm birth
- Rupture of amniotic membranes >18 hours
- Suspicion of intrauterine inflammation or infection, based on the presence of maternal fever > 39ºC or fever between 38.0 - 38.9ºC for more than 30 minutes accompanied by foetal tachycardia, maternal leucocytosis, or purulent cervical discharge.

Prevention is based on the administration of intrapartum antibiotic prophylaxis to pregnant women colonised with GBS. Prophylaxis is considered complete if at least one dose of penicillin, ampicillin or cefazolin has been administered more than 4 hours before delivery. It is important to note that prophylaxis with these antibiotics has been shown to be effective in reducing the incidence of neonatal GBS infection.

The recommended **empirical antibiotic treatment** is a combination of ampicillin and gentamicin. The **final treatment** plan, based on the results of the antibiogram, advises the use of a single antibiotic with the lowest aspect to which the germ is susceptible. The duration of treatment varies depending on the specific pathogen, but in most cases, a maximum of 7 days is recommended. (36)

Late-onset sepsis (acquired sepsis)

During the firsts months of life, preterm newborns have an immature immune system, which increases their susceptibility to invasive infections. This immaturity exposes them to environmental organisms that may be pathogenic to them. Contact with hospital personnel, family members, nutritional sources, and contaminated equipment all represent opportunities for exposure to pathogens. Hand contamination is the most common source of postnatal infection in hospitalised infants, highlighting the importance of hand hygiene. (35)

Late-onset sepsis usually starts **after the first 3 days of life**.

The incidence is not clear, as there are many differences between studies. The most common **aetiologies** are gram positive bacteria (60%), enterobacteria (30%) and fungi (7%). The global **mortality** is 8%, being higher for enterobacteria and fungi. (36)

The **clinic** is summarised in the Table 2.

The main **risk factors** are(36):

- Prematurity
- Overuse of antibiotics
- Inadequate compliance of aseptic protocols
- Intravascular catheter

Prevention is based on rigorous hand's hygiene, early oral alimentation, use of breast milk, and adherence to aseptic catheterisation protocols.

The recommended **empirical antibiotic treatment** is a combination of vancomycin and gentamicin. The **final treatment** plan, based on the results of the antibiogram, recommends the use of a single antibiotic with the lowest aspect to which the germ is susceptible. The duration of treatment depends on the specific pathogen, but in most cases, a maximum of 7 days is recommended.

In case of **fungal infection**, the use of amphotericin B deoxycholate is recommended. (36)

Table 2 *- Signs and symptoms of neonatal sepsis (36)*

SIGNS AND SYMPTOMS OF NEONATAL SEPSIS
Respiratory signs
• Respiratory difficulty: moaning, fluttering... • Persistent tachypnoea unresponsive to basic care • Apnoea lasting more than 20 seconds, repeated and requiring active intervention.
Haemodynamic signs
• Bradycardia of less than 100 beats per minute, requiring active intervention • Tachycardia • Arterial hypotension
Neurological signs
• Irritability not justified by pain • Hypotonia • Lethargy • Clinical or electrical seizures
Digestive signs
• Rejection of intakes • Poor digestive tolerance • Abdominal distension • Bloody stools
Cutaneous signs
• Jaundice • Pallor • Slowed perfusion • Purpura, pathochias
Other signs
• Hypothermia (more common in premature babies) • Hyperthermia • Hypo/hyperglycaemia • Metabolic acidosis

3.2 Neonatal respiratory distress syndrome (NRDS)

Respiratory distress syndrome (RDS), previously known as hyaline membrane disease, is a syndrome caused by **surfactant deficiency** and **pulmonary immaturity** that conduces to respiratory insufficiency. It usually occurs in preterm newborns.

3.2.1 Physiopathology

Surfactant is a liquid generated by the lungs that maintains the **opening of the airways** by decreasing the surface tension in both small airways and alveoli. This fluid facilitates breathing for newborn babies.

However, during foetal life, the developing alveoli are filled with foetal lung fluid, which does not contribute to gas exchange. Type 2 alveolar cells begin producing surfactant around 20 to 24 gestational weeks. **Sufficient surfactant should be present in the foetus by 37 weeks of gestation**. So if a baby is born prematurely, he or she may not have made enough surfactant. (37–39)

If there is **not enough surfactant**, the **alveoli collapse** every time the baby breathes. This causes a reduction in functional residual capacity (FRC), which compromises ventilation and alters the ventilation-perfusion coupling due to appearance of atelectasis. The collapsing alveoli also induce damage to lung cells, which may aggregate within the alveoli and affect breathing.

The baby has to work harder after each breath to try to reinflate the collapsed airways. As the baby's lung function deteriorates, oxygen intake decreases, which can result in **cyanosis**. The increased presence of carbon dioxide in the blood can cause **acidosis** (increased acid in the blood), which can increase pulmonary vascular resistance and favour the development of a right-left shunt, increasing **hypoxaemia**. It can also have an impact on other organs in the body. If it is left untreated, the baby becomes exhausted trying to breathe and over time gives up. The use of a ventilator becomes necessary to sustain respiration. (40)

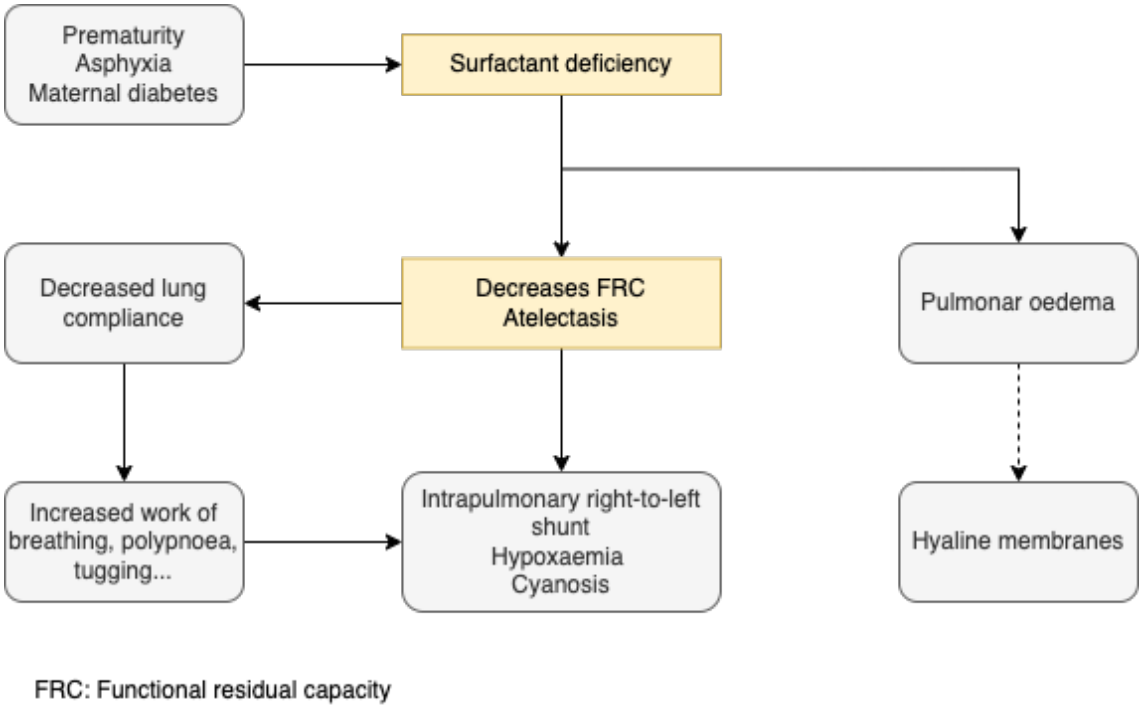


Figure 8 - Pathophysiology and clinical manifestations of NRDS (40)

3.2.2 Epidemiology

It is the **most common complication of prematurity**.

The **incidence** and severity of NRDS increases with decreasing gestational age and birth weight. Other **risk factors** include white race, male sex, maternal diabetes, perinatal hypoxia and ischaemia, and caesarean section.(41,42)

In recent years, the use of steroid injections has reduced the number of premature babies born with NRDS. (40) Steroid drugs, also known as corticosteroids, are synthetic versions of naturally occurring human hormones. When steroid injections are given to expectant mothers, the drugs are carried through the bloodstream to the body and lungs of the foetus. An antenatal course usually consists of two injections given 24 hours apart. When given between 25 and 33 weeks of pregnancy, steroids can significantly speed up the development of the foetal lungs, improving the chances of survival for many premature babies. (43)

NRDS occurs in **the 60-75% of infants born before 28 weeks of pregnancy**, in the **50% of infants born between 28 and 32 weeks of pregnancy** and less than the 5% in those born after the 36 weeks. (6,44,45)

3.2.3 Clinic

Currently, the clinical picture is very limited due to the early treatment received by these patients, which has altered the natural course of the disease, reducing clinical symptoms and mortality.

Respiratory distress begins in the **delivery room or in the first hours of life**, and it usually worsens in the first 48-72 hours of live.

Respiratory distress can be moderate or severe with **polypnea**, **moaning**, **nasal flaring**, **cyanosis**, and **retractions**. The characteristic expiratory moan is due to the passage of exhaled air through the semi-closed glottis – it is semi-closed in an attempt to maintain adequate alveolar volume and avoid alveolar collapse. (37) Restrictions are caused by the elasticity of the neonatal thorax and the generation of high intrathoracic pressures necessary to expand the inelastic lungs.

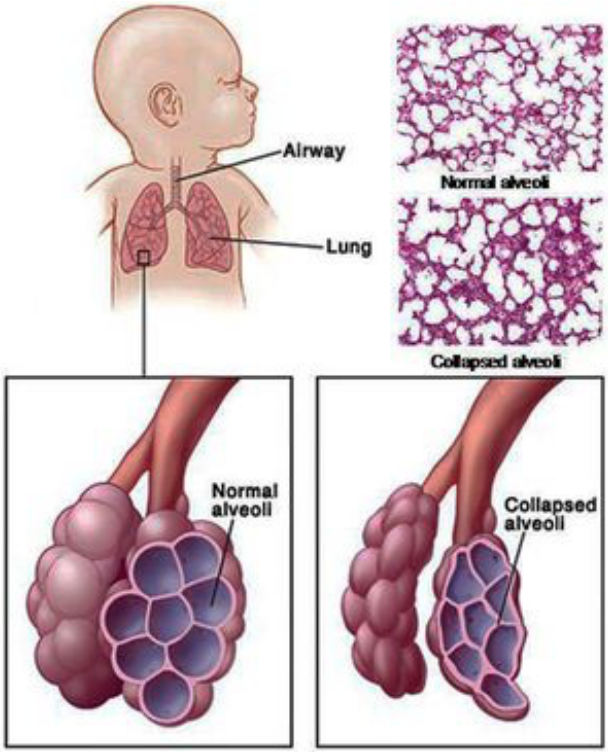


Figure 9 *- Illustration of physiopathology of NRDS (46)*

3.2.4 Differential diagnosis

The initial differential diagnosis of respiratory difficulty in the newborn is pneumonia, transient tachypnea of the newborn and NRDS. Respiratory difficulty can also be associated with some very unusual causes, such as airway or lung abnormalities or congestive heart failure.

Pneumonia is one of the most common infections in newborn babies. The infection is acquired during the prenatal period, at birth or in the early neonatal period.

Sometimes the infection and NRDS occur simultaneously, making the differential diagnosis very difficult.

3.2.5 Prevention

Lack of antenatal care increases the risk of death or severe morbidity. **General measures** to reduce preterm birth include prevention of teenage pregnancy, appropriate spacing of pregnancies, avoidance of unnecessary caesarean sections, early screening for preeclampsia and treatment with low-dose aspirin in women at risk, and single embryo transfer when in vitro fertilisation is used.

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome, make five **recommendations to prevent preterm birth** (and consequently RDS): (47)

- Mothers at high risk of preterm birth < 28-30 weeks of gestation should be transferred to perinatal centres experienced in the management of RDS.
- In women with a singleton pregnancy and a short cervix at mid-pregnancy or a previous preterm birth, **vaginal progesterone treatment** should be used to increase gestational age at delivery and reduce perinatal mortality and morbidity.
- In women with symptoms of preterm labour, cervical length and accurate biomarker measurements should be considered to **avoid unnecessary use of tocolytics and/or antenatal steroids**.

- Clinicians should offer a single course of **antenatal corticosteroids** to all women at high risk of preterm birth, from the time the pregnancy is considered potentially viable until 34 completed weeks of gestation, ideally at least 24 hours before delivery.
- A single repeat course of steroids may be given if there is risk of preterm birth before 32 weeks of gestation if the first course was given at least 1-2 weeks earlier.

3.2.6 Delivery room stabilisation

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome, make these **recommendations for stabilization in the labour room** (47):

- **Delay cord clamping for at least 60 seconds**, especially in stable preterm infants.
- Use a **T-piece** device rather than bag and mask.
- Stabilise spontaneously breathing preterm infants with **CPAP**. If apnoeic, start mask ventilation/inflations with an initial CPAP pressure of 6–8 cm H_2O and peak inspiratory pressures of 20-25 cm H_2O.
- Oxygen for resuscitation should be controlled using a blender. Start with FiO_2 of 0.30 for babies <28 weeks, 0.21–0.30 for those 28–31 weeks, and 0.21 for 32 weeks and older. Adjust FiO_2 guided by pulse oximetry, aim for SpO_2 of 80% or more by 5 minutes of age.
- Intubation should be reserved for babies who do not respond to positive pressure ventilation via face mask or nasal prongs.
- **Plastic bags or occlusive dressings**, **radiant warmers**, and **humidified gas** should be used during stabilisation for babies <32 weeks of gestation to reduce the risk of hypothermia.

3.2.7 Supportive care

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome, make the following **recommendations for supportive care in preterm infants with NRDS** (47):

- Maintain body temperature between 36.5°C and 37.5°C.
- Start parenteral nutrition from birth, with initial starting fluids of around 80 ml/kg/day, restricting sodium intake during the first few days.
- Start enteral feeding with breast milk from day 1 if the baby is stable.
- Use antibiotics judiciously and stop early when sepsis is ruled out.
- Monitor blood pressure regularly, aim for normal tissue perfusion, use inotropes if deemed necessary (ECHO recommended), and maintain haemoglobin within acceptable range.

3.2.8 Treatment

The aim of modern RDS management is to **maximize survival** while **minimizing complications.**

Oxygen supplementation over stabilization

In preterm babies receiving oxygen, the **target saturation should be between 90% and 94%,** so the alarm thresholds should be set at 89% and 95%.

Due to the high risk of having retinopathy of prematurity (ROP) in preterm infants, it is important to have protocols for screening and treating preterm babies for ROP.(47)

Surfactant administration

Surfactant is not administrated to all newborns with RDS. If it is administrated, it should be given early in the course of the disease. These are the **criteria recommended for surfactant administration** by the European Consensus Guidelines on the Management of Respiratory Distress Syndrome (47):

- Preterm babies < 30 weeks of gestation requiring intubation for stabilization.
- Worsening babies with RDS if FiO_2 > 0.30 on CPAP pressure ≥ 6 cm H_2O or if lung ultrasound suggests surfactant requirement.
- A second and occasionally a third dose of surfactant should be given if there is persistent evidence of RDS, such as persistent high oxygen requirements and other problems have been excluded.

It is recommended the use of natural surfactant given by LISA technique (less invasive surfactant administration) when the baby is on CPAP. The LISA technique uses a thin catheter for surfactant administration, and completely avoids “bagging”, allowing the infant to maintain spontaneous breathing on CPAP while surfactant is gradually delivered in small aliquots.

3.2.9 Prognosis

The prognosis for infants managed with antenatal steroids, respiratory support, and exogenous surfactant therapy is excellent. Mortality is less than 10%, with some studies showing survival rates of up to 98% with advanced care.

The improved survival in developed countries contrasts sharply with babies who received no intervention in low-income countries, where the mortality rate for premature infants with RDS is significantly higher, sometimes approaching 100%.(48)

3.2.10 Complications

Acute complications of positive pressure ventilation or invasive mechanical ventilation include air leak syndromes such as pneumothorax, pneumomediastinum, and pulmonary interstitial emphysema.

Bronchopulmonary dysplasia (BPD) is a chronic complication of RDS. Its physiopathology, clinical presentation and management are discussed in section 3.1.5.

Another complication can be neurodevelopmental delay, especially in infants who have had prolonged mechanical ventilation. The incidence of cerebral palsy is also increased in infants with RDS, with the incidence decreasing with increasing gestational age. The duration of mechanical ventilation correlates with increased rates of both cerebral palsy and neurodevelopmental delay.(37)

3.3 Mechanical ventilation

3.3.1 Concepts

Mechanical ventilation can be delivered to the patient by invasive or non-invasive methods. There are some variables that need to be considered for effective implementation of mechanical ventilation, which are more important and more commonly used in invasive ventilation. (49)

- **Tidal volume**: is the volume of air delivered to the lungs by the ventilator with each breath. It is measured in millilitres.
- **Respiratory rate:** is set according to the desired minute ventilation.
- **Minute ventilation:** is the product of the respiratory rate and the tidal volume. It is expressed in litres per minute. It is important to provide an adequate minute ventilation to allow the patient to compensate for metabolic demands.
- **PEEP** (Positive end-expiratory pressure): is the pressure in the alveoli above atmospheric pressure at the end of expiration. The PEEP delivered by mechanical ventilation allows the delivery of positive pressure at the end of expiration to prevent the unstable lung units from collapsing. It is measured in cmH_2O.
- **FiO_2** (Fraction of inspired oxygen)
- **PIP** (Peak inspiratory pressure): Peak airway pressure is a measure of the maximum pressure felt by the airways during inspiration. In the passive patient, peak pressure, depends on the respiratory rate, tidal volume, and inspiratory flow rate in volume-cycled modes of mechanical ventilation. In the awake and active patient, the patient's effort contributes to the peak pressure. It is measured in cmH_2O.
- **Flow rate:** is the maximum flow at which a set tidal volume of breath is delivered by a ventilator.

- **Plateau pressure:** is the pressure that is applied by the mechanical ventilator to the small airways and alveoli. Plateau pressure is measured at the end of inspiration.

We can talk about two different types of mechanical ventilation, the **non-invasive**, where there is no endotracheal intubation; and the **invasive**, where there is endotracheal intubation.

3.3.2 Non-invasive mechanical ventilation (NIV)

CPAP (continuous positive airway pressure)

CPAP is a type of positive airway pressure that **delivers a set pressure to the airways** that is maintained throughout the respiratory cycle, **both during inspiration and expiration**. This pressure keeps the airways open in people who breath spontaneously – patients have to initiate all their breaths. The use of CPAP maintains PEEP, can reduce atelectasis, increase alveolar surface area, improve V/Q (ventilation-perfusion) matching and therefore improves oxygenation.(50,51)

Contraindications (51)

CPAP cannot be used in patients who do not breath spontaneously. The following are relative contraindications to CPAP:

- Uncooperative or extremely anxious patients
- Reduced consciousness and inability to protect their airway
- Unstable cardiorespiratory status
- Trauma or burns to the face
- Facial, oesophageal, or gastric surgery
- Air leak syndrome (pneumothorax with bronchopleural fistula)
- Copious respiratory secretions

- Severe nausea with vomiting
- Severe air trapping diseases with hypercarbia asthma or chronic obstructive pulmonary disease (COPD)

Complications

Side effects of CPAP treatment may include (51):

- Nasal congestion, runny nose, dry mouth, or nosebleeds. Humidification can often help with these symptoms.
- Skin irritation and redness. This can be minimized with the right size mask and cushion.
- Abdominal distension or sensation of bloating, rarely leading to nausea.

Equipment

CPAP therapy uses machines specifically designed to deliver a flow of constant pressure flow. Some CPAP machines have other features as well, such as heated humidifiers. Newborn babies do better when the air delivered is heated and humidified.

CPAP can be administered in several ways depending on the mask interface used:

- Nasal CPAP: Nasal prongs that fit directly into the nostrils or a small mask that fits over the nose. It is the most used in neonates.
- Nasopharyngeal (NP) CPAP: Administered via a nasopharyngeal tube, which is an airway that is passed through the nose and ends in the nasopharynx.
- CPAP via face mask: A full face mask is placed over the nose and mouth to create a thigh seal.

A CPAP machine also includes straps to help position the mask, a hose or tube that connects the mask to the machine's motor, a motor that blows air into the tube, and an air filter to purify the air that enters the nose.(51)

Figure 11 - Illustration of CPAP in neonates(52)

CPAP in RDS

CPAP is recommended as **the first choice for respiratory support**.

Recommendations from the European Consensus Guidelines on the Management of Respiratory Distress Syndrome (47):

- CPAP should be started from birth in all babies at risk of RDS, such as those < 30 weeks of gestation who do not require intubation for stabilisation.
- The interface of CPAP should be short binasal prongs or mask with a starting pressure of approximately 6-8 cmH_2O.
- Bilevel positive airway (BIPAP) devices offer no advantage over CPAP.

3.3.3. Invasive mechanical ventilation

There are a lot of different modalities of invasive mechanical ventilation.
Only the two modalities related to this project will be discussed: **assist-control volume guarantee ventilation** and **pressure-support ventilation.**

Assist-control ventilation

Assist-control volume guarantee ventilation (ACVGV) is a combination mode of ventilation in which the **current tidal volume is delivered in response to the inspiratory effort or if no patient effort occurs within a set period of time**. The period is determined by the backup respiratory rate set on the ventilator. When there is an inspiratory effort from the patient, the ventilator senses this as a trigger and initiates another controlled breath.

All breaths are done by the ventilator, the patient cannot take spontaneous breaths. (53)

The advantage of ACV (assist-control ventilation) is that it significantly reduces work of breathing and decreases myocardial oxygen demand. The disadvantages of ACV in the active patient are that it is less comfortable than spontaneous breathing and that it can induce respiratory alkalosis and breath-stacking.

With volume ACV, the volume is set by the professional, so it is constant, but the airway pressure varies. When patients with severe hypoxaemia require high PEEP and FiO_2 settings to maintain adequate oxygenation, the airway pressures that are generated to deliver the desired tidal volume increase. This increasing pressure can be measured as the peak inspiratory pressure or the plateau pressure, all of which attempt to describe the pressures that are transmitted through the airways at different levels and at different points in the respiratory cycle. (49)

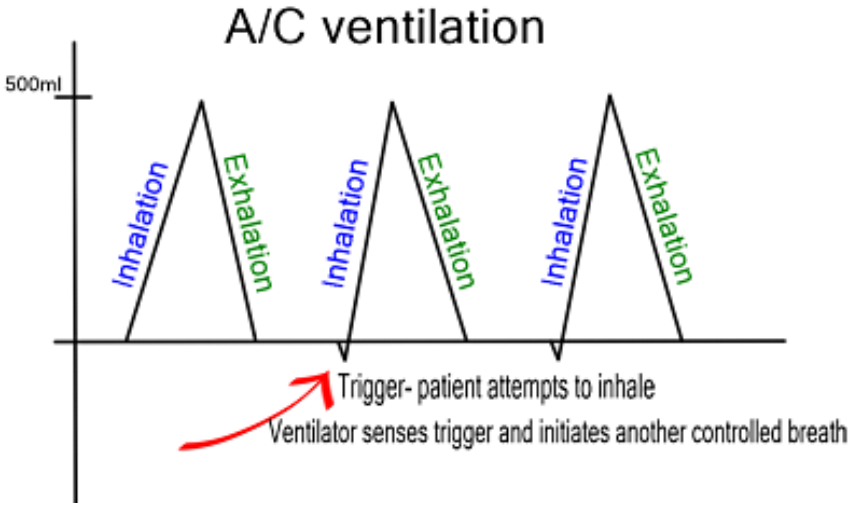


Figure 12 *- Assist-control ventilation curves (54)*

Pressure support ventilation

Pressure support ventilation (PSV) is used in patients who are awake enough to breathe spontaneously. It augments the patient's spontaneous inspiratory efforts with the selected level of positive airway pressure. (49) The ventilator does not do any of the breathing, the patient starts all the breaths, and the ventilator helps with each one with a certain pressure. The **beginning and end of the breaths are therefore determined by the patient's effort**. (53)

Inspiratory pressure is delivered until the flow decreases to a predetermined level (usually 25% of peak flow). PSV allows the clinician to control the desired pressure support, PEEP, and FIO_2.

As this mode of ventilation does not guarantee a tidal volume, pressure support must be titrated to help the patient achieve an adequate tidal volume. However, any change in lung compliance or airway impedance will result in a change in tidal volume. A certain level of pressure support is required to overcome the resistance of the ventilator circuit and endotracheal tube. Pressure support above that required to overcome the resistance will add to the tidal volume achieved. (49)

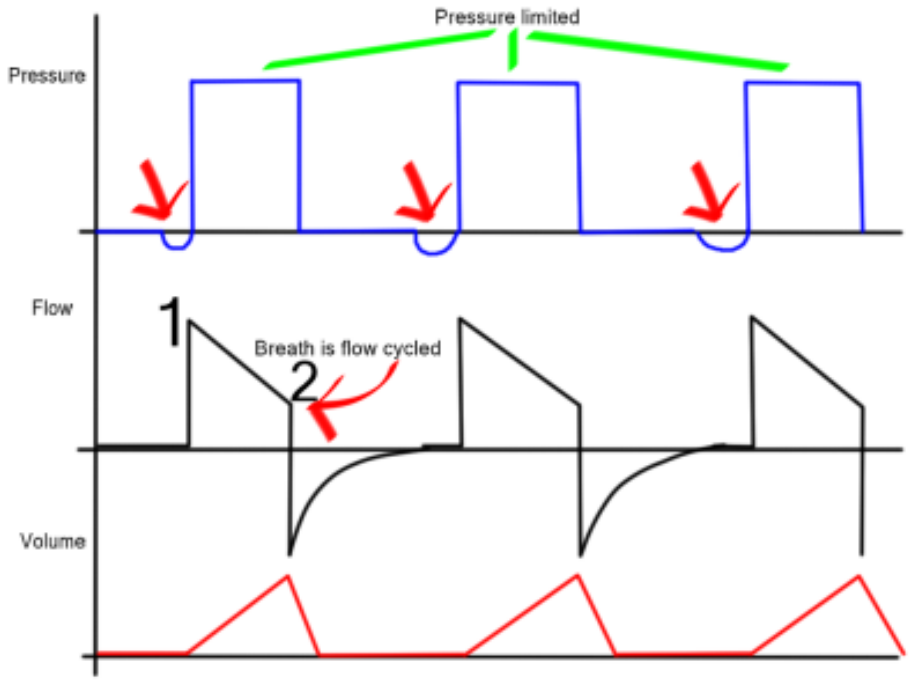


Figure 13 *- Pressure support ventilation curves (55)*

Weaning of mechanical ventilation

Weaning is the **transition from ventilatory support to completely spontaneous breathing**, during which time the patient assumes the responsibility for effective gas exchange as positive pressure support is withdrawn.

Weaning is usually started when the patient meets certain criteria. For example, spontaneous breathing is a prerequisite for weaning to begin.

There is no standard method for weaning (56), but two of the most commonly used methods are those mentioned above: volume assist-control ventilation and pressure-support ventilation.

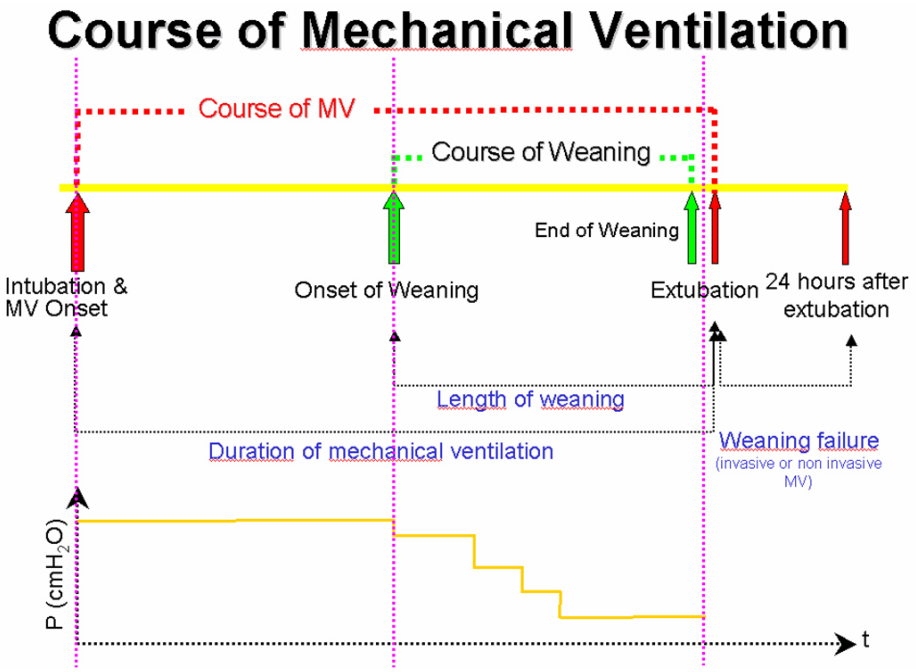


Figure 14 *- A schematic of the time and pressure courses of mechanical ventilation, along with the defined phases, in a NICU patient. (56)*

Extubation of mechanical ventilation

Extubation is the **removal of the endotracheal tube**. There are several criteria for extubation, including spontaneous ventilation, haemodynamic stability, intact airway reflexes, and manageable airway secretions. **After extubation, CPAP** is applied, so that the patient still has some support.

Extubation failure has been variably defined as reintubation within 24-72 hours. We can define the extubation failure according to when it occurs:

- Early extubation failure is defined as that which occurs within 6 hours after extubation
- Intermediate extubation failure is that which occurs between 6 and 24 hours after extubation
- Late extubation failure is defined as that which occurs between 24 and 48 hours after extubation. (56)

The **Extubation Readiness Test (ERT)** is a formal test of spontaneous breathing to assess readiness for removal of the endotracheal tube and/or ventilatory support. One way of doing this is to assess spontaneous breathing be evaluated for 2 hours on CPAP ≤5 cmH2O or T-piece (ZEEP). Criteria for failure, both subjective and objective, are suggested in Table 2.

Criteria for Extubation Readiness Test Failure

Proposed Criteria for Failure During 2 Hours on CPAP < 5 cmH_2O or T-piece

Clinical Criteria:

- Diaphoresis
- Nasal flaring
- Increasing respiratory effort
- Tachycardia (increase in HR > 40 bpm)
- Cardiac arrhythmias
- Hypotension
- Apnea

Laboratory Criteria:

- Increase of $P_{ET}CO_2$ > 10 mmHg
- Decrease of arterial pH < 7.32
- Decline in arterial pH > 0.07
- PaO_2 < 60mmHg with an FiO_2 > 0.40 (P/F O_2 ratio < 150)
- SpO_2 declines > 5%

Table 3 *- Criteria for extubation Readiness Test Failure (56)*

Invasive mechanical ventilation in RDS

Despite best efforts to maintain as many preterm babies as possible on NIV, approximately **half of babies < 28 weeks will require invasive mechanical ventilation**. (57)

The aim of invasive mechanical ventilation is to achieve “acceptable” blood gases by ventilating at optimal lung volumes (while avoiding overdistension and atelectasis).

The initial tidal volume is usually set at around 5 ml/kg (58) with a maximum PIP of 25-30 cmH2O. Adjustments to the initial tidal volume have to be done, according to assessment of work of breathing and blood gas evolution. Required tidal volumes vary around 5-7 ml/kg, the range tending to increase with increasing postnatal age.

PEEP should be adjusted to keep the lung open by finding a point where FiO_2 is at its lowest with haemodynamic stability and acceptable blood gases.

Once stabilised on invasive mechanical ventilation and with evidence of spontaneous respiratory effort, clinicians should immediately start planning for weaning to NIV. Some infants require a very short period of ventilation, particularly those with RDS following surfactant therapy, and early extubation of even the smallest babies who achieve low ventilator settings should be encouraged. (47)

Infant’s size, absence of growth restriction, oxygen requirements and blood gases can all help to determine the success of extubation. (59) Delaying extubation does not improve the chances of success.

When weaning from invasive mechanical ventilation, it is reasonable to tolerate a modest degree of hypercarbia, provided the pH remains above 7,22.

Caffeine (20 mg/kg loading, 5-10 mg/kg maintenance) should be used to facilitate weaning from MV.(60)

4. JUSTIFICATION

Neonatal respiratory distress syndrome is the most common complication of prematurity. Its incidence increases with the lower gestational age, so that the babies most affected are those born at less than 32 weeks' gestation (40,61). In general, these are the babies with the greatest complications of prematurity, so it is important to try to reduce their morbidity and mortality.

Up to 40%(61) of these premature babies with NRDS require invasive mechanical ventilation to manage the syndrome. According to some studies and the European NRDS guidelines (47), it is recommended that babies are intubated for as short a time as possible.

Weaning, the step before extubation, is **essential for safe extubation**. Although there are two main weaning protocols, there are **no studies** to show which one is better for these neonates.

Demonstrating which of the two weaning protocols currently used is more effective is essential to reduce the morbidity and mortality associated with this syndrome.

The aim of this research is to determine which of the two protocols results in fewer reintubations and shorter weaning times. Studies suggest that a lower number of these variables may lead to a lower incidence of complications associated with NRDS, thereby reducing associated morbidity and mortality. If this research demonstrates that one protocol is superior, it could be implemented to make weaning more effective and reduce complications in premature babies with NRDS.

This study is also relevant because, although there are some studies on weaning in adults, there is practically no literature on these issues in the neonatal population. It is inappropriate to apply adult data to premature neonates due to the immature control of ventilation, the unique lung physiology, ventilation mechanics, and types of lung disease found in newborns.

5. HYPOTESIS

The assumptions leading to the start of this study are as follows:

5.1 Main hypothesis:

Using **pressure support ventilation** for the weaning in extremely and very preterm neonates with newborn respiratory distress syndrome on invasive mechanical ventilation, reduces the number of reintubations, in comparison with the use of **assist control volume guarantee ventilation**.

5.2 Secondary hypothesis:

Using **pressure support ventilation** for the weaning in extremely and very preterm neonates with newborn respiratory distress syndrome on invasive mechanical ventilation, reduces the time of weaning, in comparison with the use of **assist control volume guarantee ventilation.**

6. OBJECTIVE

The proposed project has the following objectives:

6.1 Main objective:

To compare the number of reintubations of **pressure support ventilation** and **assist control volume guarantee ventilation** when used for weaning**,** in extremely and very preterm neonates with newborn respiratory distress syndrome on invasive mechanical ventilation.

6.2 Secondary objectives:

To compare the time of weaning of **pressure support ventilation** and **assist control volume guarantee ventilation** when used for weaning, in extremely and very preterm neonates with newborn respiratory distress syndrome on invasive mechanical ventilation.

7. SUBJECTS AND METHODS

7.1 Study design

This project is designed as a **multicentre clinical trial** to compare two different modalities of weaning (PSV and ACVGV) in extremely and very preterm newborns with NRDS. As it will be multicentric, it will be conducted in 5 different centres over Catalonia.

A **consecutive stratified sampling** will be done, participants will be selected when they are on invasive mechanical ventilation due to NRDS and meet the inclusion criteria. The two groups will be created by **randomization** in a ratio 1:1, so that there is **equivalence** between them.

Regarding the masking method, it will be **simple blinded**, as the preterm newborns will not know which protocol they are assigned to.

7.2 Study population

Inclusion criteria

- Preterm neonate, born at less than 32 weeks of gestation.
- Must be on invasive mechanical ventilation due to neonatal respiratory distress syndrome.
- Informed consent signed by parent or legal guardian.

Exclusion criteria

- Any congenital malformations
- Any chromosomopathies
- Any cardiopathies
- Any neurological malformations

These criteria have been selected because all of these pathologies can affect the patient's respiratory pattern, so it is possible that newborns with these criteria may have different management necessities, more time on mechanical ventilation, or more complications related to their underlying pathology.

Withdrawal criteria

- **Request to revoke consent for the study:** the parents or legal guardians of the neonate can express voluntary decision to be excluded from the study at any point. (see Annex 6)
- **Neonates' death:** from enrolment until the end of the follow-up period.

7.3 Sampling

7.3.1 Sample size

We estimated the sample size using the free online software GRANMO, and the setting for two independent proportions.

In the view of the literature published so far, the proportion of reintubation in preterm newborns that are on invasive mechanical ventilation is 16% (studies differ between 12% and 20%, an average has been made).(62,63)

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **271** subjects are necessary in first group and **271** in the second to recognize as statistically significant a difference greater than or equal to 0.1 percent units. A proportion in one of both groups has been estimated to be 16%. It has been anticipated a drop-out rate of 5% (0,05).

7.3.2 Sample collection

As previously mentioned, the sampling method selected for the study will be a **consecutive sampling**. The choice to enter the study will be offered to the parents or legal guardians of preterm newborns that are in NICU on invasive mechanical ventilation due to NRDS.

Regarding sample collection, each hospital will be responsible for the recruitment and follow-up of its own patients.

7.3.3 Estimated time of recruitment

Recruitment will be stratified according to the proportion of preterm newborns in each hospital attends.

According to the last study on the incidence of prematurity stratified by hospital done in Catalonia (64), the 5 hospitals with the highest incidence of extremely and very preterm newborns will be included in the study. They will be named in numbers from 1 to 5.

- Hospital 1 attends 386 extreme and very preterm babies per year
- Hospital 2 attends 333 extreme and very preterm babies per year
- Hospital 3 attends 208 extreme and very preterm babies per year
- Hospital 4 attends 137 extreme and very preterm babies per year
- Hospital 5 attends 106 extreme and very preterm babies per year

The total number of extreme and very preterm babies born in these 5 hospitals per year is 1.170.

The incidence of NRDS in extremely preterm newborns is approximately 70% and the incidence in very preterm newborns is about 50% (6,44,45), so an incidence of 55% have been used to estimate the time of recruitment. (The calculation has been made with the proportion of extremely and very preterm newborns obtained from the last incidence study carried out in Catalonia (6)).

Thus, there are approximately 644 newborns with NRDS per year in these 5 hospitals.

The percentage of preterm infants born at less than 32 weeks' gestation with NRDS requiring invasive mechanical ventilation is 40%, according to the latest report of the Spanish Society of Neonatology (seNeo), carried out in 2021 (61).

So, extrapolating these data, there are 257 neonates with NRDS on invasive mechanical ventilation per year in these 5 hospitals.

To carry out the study, we need a total of 542 participants, 271 for each protocol.

So, **it will take 26 months to obtain the sample (two years and two months).**

The **final stratified recruitment** will be:

- 179 newborns from Hospital 1 (33%)
- 152 newborns from Hospital 2 (28%)
- 97 newborns from Hospital 3 (18%)
- 65 newborns from Hospital 4 (12%)
- 49 newborns from Hospital 5 (9%)

7.3.4 Randomization and masking

The recruited patients of each hospital will be **randomly divided in two groups**, through an electronic randomization statistical software that will generate a specific identification patient number for the study and will perform a randomization of the patients. The ratio will be 1:1.

Given the nature of the study, it will be a **single blinded trial**, since the newborns do not know which of the two protocols is applied to them.

7.4 Variables and measurements

Independent variable

The independent variable is the **invasive mechanical ventilation protocol** used during the weaning. It is conceived as a **dichotomous qualitative nominal variable** and is expressed as PSV/ACVGV:

- PSV: Pressure support ventilation
- ACVGV: Assist control volume guarantee ventilation

Dependent variables

There are two dependent variables: **number of reintubations** and **time of weaning**.

The **number of reintubations** is the main dependent variable. It is a **discrete quantitative variable**. The higher the number of reintubations, the higher the risk of complications, so it is a good variable to determine which protocol is more effective. Extubation failure is defined as reintubation within 24-72 hours, so the number of reintubations will be counted for the first 72 hours after the extubation.

The **time of weaning** is the secondary dependent variable. It is a **continuous quantitative variable**. It is counted from the moment the weaning is started until the extubation is executed. The longer this time is, the greater the risk of complications arising from invasive ventilation that the child may have, so it is a good variable to determine which protocol is more effective.

Covariates

- **Gestational age at birth/type of preterm:** once is born, the baby will be classified into one of these categories. It is a *dichotomous qualitative ordinal variable:*
  - Extremely preterm (< 28 weeks of gestation)
  - Very preterm (28-32 weeks of gestation)
- **Birthweight:** it is a *continuous quantitative variable* measured in grams.
- **Sex:** it is a *dichotomous qualitative nominal variable*. Categorized as men or women.
- **CPR after birth:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

- **5-minute Apgar score** (see Annex 1)**:** It is a quantitative variable, but categorized in the following intervals, resulting in a *polychotomous qualitative ordinal variable:*
  - Apgar 0-3
  - Apgar 4-6
  - Apgar 7-10

- **Risk factors of prematurity:**

  - **Previous preterm birth:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Second trimester miscarriage (> 16 weeks):** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Multiple pregnancy:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Chorioamnionitis**: it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Premature rupture of membranes** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Maternal age:** it is a *continuous quantitative variable*. Measured in years

  - **Maternal size:** it is a continuous quantitative *variable*. Measured in cm.

  - **Cervical surgery:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Congenital uterine anomaly:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Diabetes or gestational diabetes:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

  - **Sexually transmitted infection:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

- **Smoking during pregnancy:** it is a *dichotomous qualitative nominal variable.* It will be expressed as yes or no.
- **Consuming alcohol or other toxics during pregnancy:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.
- **Short intragestational period:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.
- **Extrauterine infection:** it is a *dichotomous qualitative nominal variable*. It will be expressed as yes or no.

All these covariates will be obtained from the clinical history of the mother and the newborn, as all these information will be obtained before the recruitment of the patient in the study. Special importance will be given to the gynaecological clinical history of the pregnancy.

Table 4 *- Summary table of variable*

	Variable	Type of data	Categories or values
Independent variable	Protocol of invasive mechanical ventilation	Dichotomous qualitative nominal	PSV / ACVGV
Dependent variables	Number of reintubations	Discrete quantitative	Numerical
	Time of weaning	Continuous quantitative	Numerical (days)
Covariates	Sex	Dichotomous qualitative nominal	Men / Women
	Type of preterm	Dichotomous qualitative ordinal	Extremely preterm / Very preterm
	Birthweight	Continuous quantitative	Numerical (grams)
	CPR after birth	Dichotomous qualitative nominal	Yes / No
	5-minute Apgar score	Polychotomous qualitative ordinal	0-3 / 4-6 / 7-10
	Risk factors of prematurity		
	Previous preterm birth	Dichotomous qualitative nominal	Yes / No
	Second trimester miscarriage	Dichotomous qualitative nominal	Yes / No

	Multiple pregnancy	Dichotomous qualitative nominal	Yes / No
	Chorioamnionitis	Dichotomous qualitative nominal	Yes / No
	Premature rupture of membranes	Dichotomous qualitative nominal	Yes / No
	Maternal age	Continuous quantitative	Numerical (years)
	Maternal size	Continuous quantitative	Numerical (cm)
	Cervical surgery	Dichotomous qualitative nominal	Yes / No
	Congenital uterine anomaly	Dichotomous qualitative nominal	Yes / No
	Diabetes or gestational diabetes	Dichotomous qualitative nominal	Yes / No
	Sexually transmitted infection	Dichotomous qualitative nominal	Yes / No
	Smoking	Dichotomous qualitative nominal	Yes / No
	Consuming alcohol or other toxics	Dichotomous qualitative nominal	Yes / No
	Short intragestational period	Dichotomous qualitative nominal	Yes / No
	Extrauterine infection	Dichotomous qualitative nominal	Yes / No

7.5 Study intervention

In this study there will be two different protocols applied for weaning of invasive mechanical ventilation in extremely and very preterm newborns with NRDS: PSV and ACVGV. These protocols will be applied by professional neonatologists.

When an extremely or very preterm newborn is in invasive mechanical ventilation due to NRDS and meets all inclusion criteria and any exclusion criteria, an informative document (see Annex 4) and an informed consent (see Annex 5) will be given to the parents or legal guardians to sign.

Once the newborn enters the study, the neonatologists will wait until this patient meets the **criteria to start the weaning**. These criteria will be **precisely explained** in the document given to all hospital coordinators during the formation sessions. The weaning criteria are the following:

- Clinical criteria:
    - Stable patient
    - No intercurrent process that may hinder weaning
- Respirator parameters
    - FiO2 < 40 mmHg
    - PEEP < 7 cmH_2O
    - RR < 50 rpm
    - PIP < 20 cmH_2O

When the patient meets the weaning criteria, the intervention will start. The intervention will be carried out by a neonatology expert. The patient will be randomly assigned in one of the two groups:

- Group 1: The protocol used for the weaning will be ***pressure support ventilation (PSV)***
- Group 2: The protocol used for the weaning will be ***assist control volume guarantee ventilation (ACVGV)***

Both protocols of weaning have been properly explained in section *3.3.3 Invasive mechanical ventilation.*

The patient will remain in weaning util he or she meets the **criteria for extubation.** These criteria will be **precisely explained** in the document given to all hospital coordinators during the formation sessions. The patient will be extubated to a CPAP with a nasal PEEP of 6 mmHg. The extubation criteria are the following:

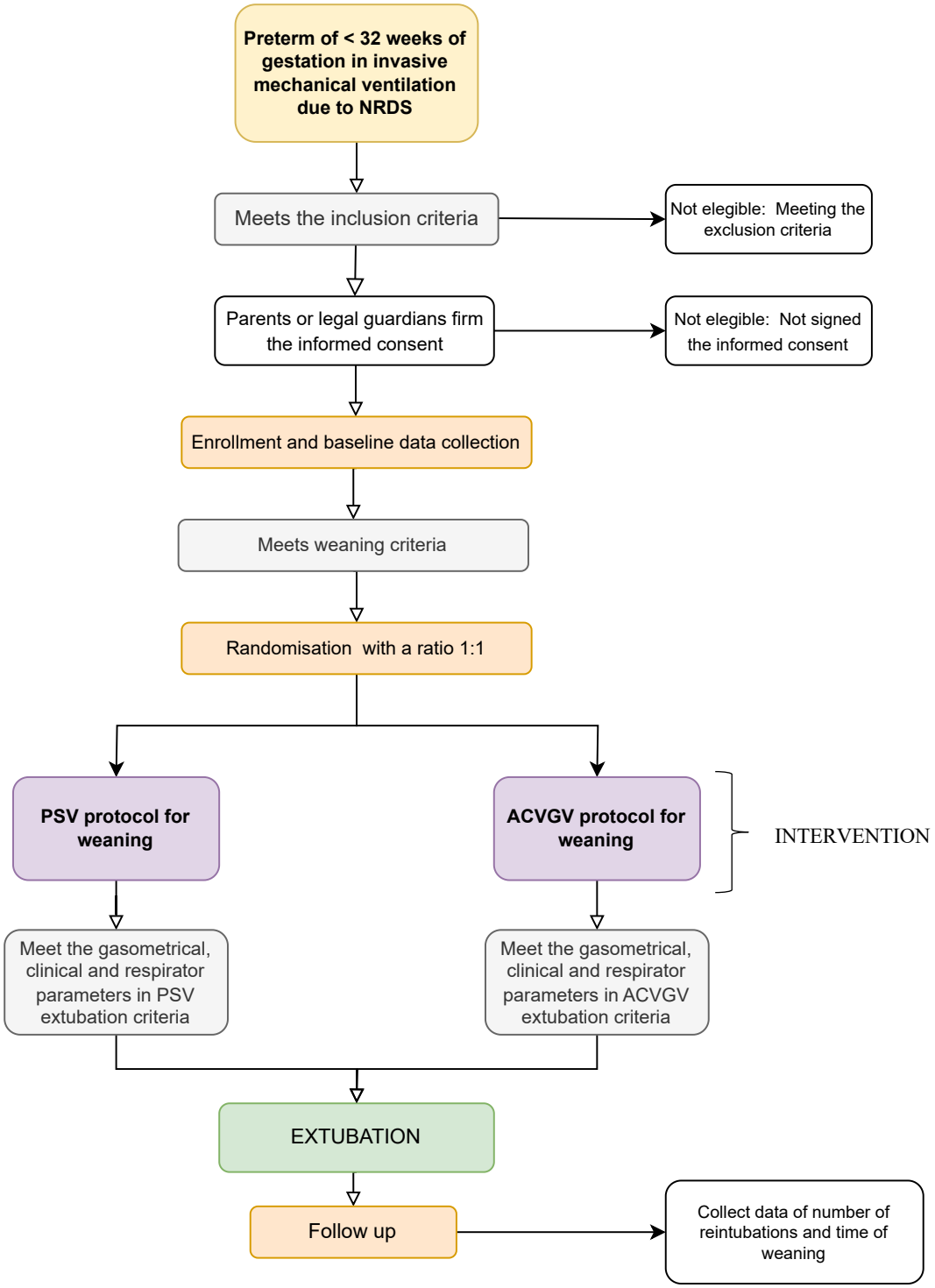
- Gasometrical criteria:
  - pH > 7,3
  - pCO_2 < 50 mmHg
  - pO_2 > 70 mmHg
  - Sat Hb 90-95% (haemoglobin saturation)
- Clinical criteria:
  - Stable patient
  - Without active infectious process
  - Without hemodynamically significant ductus
  - Neurologically capable of maintaining a patent airway
- Respirator parameters:
  - PEEP < 6 mmHg
  - FiO_2 < 30 cmH_2O
  - RR < 20 rpm
  - PIP < 20 cmH_2O
  - Tidal volume 5 ml/kg

Once the extubation is done, the patient will be **followed up for 72 hours**. If during this follow up the patient meets the **reintubation criteria**, the newborn will be reintubated and this data will be properly collected. These criteria will be **precisely explained** in the document given to all hospital coordinators during the formation sessions. The reintubation criteria are the following:

- Gasometrical criteria:
  - pH < 7,2
  - pCO_2 > 60 mmHg
  - pO_2 < 70 mmHg
  - Sat Hb < 90% (hemoglobin saturation)

- Clinical criteria:
    - Progressive increase in work of breathing.
    - Frequent apnoeas requiring positive pressure ventilation.
- Respirator parameters in NIV:
    - PEEP > 6 mmHg
    - FiO_2 > 50 cmH_2O

7.6 Flow chart



7.7 Data collection

All baseline and outcome data will be collected prospectively using a data collection form. This data form has been designed to collect all clinical and procedural information (see Annex 7) from the different NICUs participating in this project.

Each patient will be identified with a special ID to maintain anonymity, the patient's name cannot appear. Once a week, the neonatologist expert or hospital coordinator of each hospital must collect all the files gathered by the neonatologists of his/her hospital and add them to an online database. When the statistical specialist analyses the database, he/she will not know the name of the baby, or the technique used.

A **data quality control service will be contracted** to supervise the process and ensure correct data collection.

Period 1: Inclusion and baseline data

The main investigator will contact potential participants to evaluate if they meet all the inclusion criteria and any exclusion criteria. This will take place in the NICU, when there is a preterm infant with NRDS on invasive mechanical ventilation.

If the patient meets all the study criteria, an information form (see Annex 4) and an informed consent (see Annex 5) will be given to the parents after proper explanation.

When the patient is already part of the study, the researcher will proceed with the collection of baseline data, corresponding to the covariates.

Period 2: Intervention period

A baseline researcher, not involved in the outcome assessment, will be responsible for assigning the ID code to each participant. In addition, this

researcher will distribute to the neonatologist the randomised allocation prepared by the biostatistician, indicating the protocol he/she will use.

During the intervention, the baseline researcher must ensure that all dependent variables related to the intervention are collected.

Period 3: Follow up

After 72 hours of the intervention, the baseline researcher not involved in the outcome assessment will evaluate the dependent variable (reintubation).

Once completed, the data form must be sent to the hospital coordinator or neonatologist expert who will add the data to the general online database.

Later, when all the data from all the participants is completed, it will be sent to the statistician expert for analysis.

Figure 18 *- Summary of the data collection process*

7.8 Safety

The intervention carried out in this study does not entail any added risk to the patient, as all patients on invasive mechanical ventilation require the weaning process prior to extubation.

In this study, the intervention focuses only on the assignment of the weaning protocol. The two protocols used in the trial are those currently used in NICUs, with studies that support their use.

So, patients on the study will not have any additional risk compared to patients in the same situation outside the study.

8. STATISTICAL ANALYSIS

The analysis of the data obtained will be done by a **statistical analyst**, who will not know in which group PSV protocol was used and in which ACVGV protocol. The software used will be *Statistical Package for Social Sciences (SPSS)* software version 28.1. A p-value of < 0,05 will be considered statistically significant, defining a 95% confidence interval for all analyses.

8.1. Descriptive analysis

First, we will summarize all dependent, independent variables and covariates.

- **Qualitative variables** (protocol used, type of preterm, CRP after birth, 5-minute Apgar score and most covariates related with risk factors) will be described using **proportions.**
- **Quantitative variables** (number of reintubations, time of weaning, birthweight, maternal age, and maternal size) will be summarized by **means, standard deviation, medians, and interquartile range (IQR)**

The dependent variables are quantitative, so a comparison of medians will be made in relation to the assigned protocol, PSV or ACVGV, will be done. These descriptives will be stratified by the categories of the covariates.

8.2 Bivariate interference

Both dependent variables, number of reintubations and time of weaning, are quantitative. The relation between number of reintubations and each protocol, will be contrasted using **T-Student test**. The relation between time of weaning and each protocol will be contrasted using **Kaplan-Meier,** as it is a survival analysis.

The relation between **quantitative covariates** and each protocol, will also be contrasted using **T-Student test.**

And the relation between **qualitative covariates** and each protocol will be contrasted by **Xi-squared test** or **Fisher's exact test** (if the expected number of cases in a cell will be less than 5).

8.3 Multivariate interference

It will be necessary to do a multivariate analysis adjusting the covariates according to the independent variable with the dependent variables that can interfere in the results, to avoid possible confusion.

Poisson regression model will be used for the association between the intervention and the number of reintubations, which is a **discrete quantitative variable**.

Cox regression models will be used for the association of the intervention with the **time** of weaning, which is a **continuous quantitative variable**. It is calculated as a survival analysis.

9. ETHICAL AND LEGAL CONSIDERATIONS

Ethical principles

The study will be performed under the requirements established by the World Medical Association (WMA) in the **Declaration of Helsinki** of Ethical Principles for Medical Research Involving Human Subjects (last revision in the 64th General Assembly, Fortaleza, Brazil, in October 2013) (65). This experimental study obeys the **Principles of Biomedical Ethics from Beauchamp and Childress** from 1970, reviewed in 2009, more commonly known as the four fundamental ethical principles:

- **Beneficence and non-maleficence:** Ensuring individuals are treated ethically, their decisions are respected, and they are protected from harm is the basis of beneficence. It is an obligation to ensure their well-being. In this study, all participants will receive invasive mechanical ventilation because they need it, and both weaning protocols used in this clinical trial are approved and used in clinical practice.

- **Justice:** To ensure that all individuals benefit from the research, we have established very inclusive and exclusive criteria and carefully selected a sample that we believe will benefit most from this intervention. Following the sampling phase, we have randomly assigned the protocol to ensure equal chances for all participants to receive a specific intervention.

- **Autonomy:** The recognition that people are autonomous and entitled to their own opinions and decisions. In this study, as the participants are neonates, the parents or legal guardians will be informed in detail about the study procedures, how data will be handled, and their right to be informed or to withdraw at any moment will be respected.

  An **informative document** about the study protocol (see Annex 4) will be given to the parents or legal guardians of the patient in a language they can understand, in order to provide them with the necessary knowledge and understanding.

As this project involves neonates, parents or legally authorized representatives will be required to sign two reports: the first, giving the authorization to perform any intervention on the infant admitted to the NICU (see Annex 3); and the second, allowing the participation in our study, after providing comprehensive information. To express their agreement to participate in the study, they will sign the **informed consent form** (see Annex 5).

The autonomy of the participants is regulated by Spanish legislation: ***"Law 41/2002, November 14th, regulating patient autonomy and right and obligations of information and clinical documentation".*** (66)

Privacy and confidentiality

All personal data collected from each patient during the study will be confidential, only for purpose of research and education; moreover, all data will be analysed anonymously, in accordance with the current legislation:

- Spanish data protection legislation: **"Organic Law 3/2018, of 5 December, on Data Protection and Guarantee of Digital Rights and the royal decree 1720/2007**". (67)
- ***Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data.*** (68)

All newborns personal and clinical data collected in this study will be anonymous and confidential, as they will be identified by a **randomised code** generated by an electronic randomisation statistical software.

In addition, all data collected will **be available only to the research team** and will be used strictly for research purposes.

Comité d'Ètica i d'Investigació Clínica (CEIC)

The present project will be submitted to the CEIC of the *Hospital Universitari Dr Josep Trueta (HUJT)*, whose suggestions given will be considered and whose approval will be mandatory before the start of the study. The system of controls to be carried out during the research will be in accordance with ***Ley 14/2007, de 3 de julio, de Investigación biomédica*.** (69)

Transparency

All investigators of this study will be required to declare no conflicts of interest. They will also have to agree to publish all data and results obtained with total transparency, including unfavourable data or events.

10. WORK PLAN AND CHRONOGRAM

10.1 Participating centres

The 5 centres proposed to carry out the study are the five with the highest incidence of extremely and very preterm newborns in Catalonia, according to the last study carried out.(64) Each hospital was assigned a number from 1 to 5.

10.2 Research team members

The personal required at the different stages of the clinical trial include:

- **Main investigator (MI) and director of research:** As director of research, he or she will direct the execution of the project, ensure the correct application of the protocol and the correct storage of the data. He or she will also participate in the discussion of the results, prepare the final report of the conclusions and their subsequent dissemination through the publication of the results.
- **Study Coordinator (SC):** As coordinator, he will be responsible for supervising the proper functioning of the other participating centres.
- **Hospital Coordinators (HC) – Head of co-investigators:** Each hospital will have a coordinator who will collect the data and ensure that the protocol is carried out correctly in his/her centre. They will facilitate coordination with the main investigator.
- **Co-investigators (CI):** These include expert intensivist; paediatricians; and **neonatologist experts**. The hospital coordinator and the neonatal expert can be the same professional. There will be co-investigators in each hospital.
- **Health Care Professionals (HCP):** Include all personnel needed to carry out this clinical trial, such as nurses or anaesthesiologists.
- **Data manager (DM):** She/he will manage the data collection during the study. He/she will be responsible for data processing, quality control and report writing for interim and final data analysis.

- **Statistical Specialist (SS):** The professional who will carry out the statistical analysis.
- **Other staff:** computer scientist, cleaning stuff and other personal working in the hospital or involved in the process.

10.3 Study stages

The hole study will have an estimated duration of 44 months, which is equivalent to **3 years and 8 months**. The steps in this clinical trial will be performed in the following order, grouped into 6 stages, each consisting of different activities:

STAGE 0: Elaboration of the protocol and study design (4 months: September – December 2023)

1. **First session** (September 2023, completed): To discuss the project and to identify the gaps in information in this field of study.
2. **Bibliographical research and protocol elaboration** (September – November 2023): Includes the literature review and all practical considerations to elaborate the protocol. This phase will be carried out by the research members.
3. **Contact with the participating hospitals** (December 2023): the MI and SC will propose to the selected hospitals if they want to participate in the study. The protocol will be evaluated by the neonatologists, who will decide if they want to participate.

STAGE 1: Ethical approval (3 months: December 2023 – February 2024)

4. **Ethical evaluation and approval:** Presentation of the protocol to the research ethics committee (CEIC) of HUJT.

   Any suggestions will be considered and modifications on the protocol will be made if necessary.

   The length of this stage will depend on how long it takes for the CEIC to approve the study, an approximation of 3 months has been made.

STAGE 2: Coordination and health professionals training (2 months: March – April 2024)

5. **First meeting with the research team** (March 2024): During this month, a date will be set for the first face-to-face meeting between the main investigator and the hospital coordinators of each centre. At this meeting, the different phases of the study, the timetable, the inclusion and exclusion criteria for patients, and the role of each investigator will be reviewed. An e-mail and/or telephone number will also be provided for better coordination. After this meeting, each hospital coordinator will be asked to hold a second meeting with all the co-investigators at his or her centre to provide them with the same information.

6. **Formation sessions** (April 2024): An online meeting will be held with the whole team to provide theoretical training on neonatal resuscitation and neonatal mechanical ventilation. Particular emphasis will be placed on invasive mechanical ventilation and weaning. During this meeting, a consensual and detailed document will be sent to the hospital coordinators of each centre with the values of each parameter of the ventilator necessary for both the initiation of weaning and extubation. It will also include the clinical and gasometrical criteria for weaning, extubation and reintubation.

   The aim of this training is to homogenise the process and reduce differences in the results between centres.

7. **Creation of a database** (April 2024)**:** A computer scientist will be hired to create a database, so that the data collected before, during and after the intervention can be correctly recorded.

STAGE 3: Sample recruitment, intervention, and data collection (27 months: May 2024 – July 2026)

8. **Sample recruitment:** As mentioned above, a consecutive stratified sampling method of extremely and very preterm newborns with NRDS that are on invasive mechanical ventilation, admitted to the NCIU of the participating hospitals will be carried out. Each co-investigator at each centre will be responsible for enrolling patients who meet all the inclusion criteria and any of the exclusion criteria, after the parents or legal guardians have signed the informed consent form (see Annex 5). Each participant will be randomised to one of the intervention groups of the clinical trial. The hospital coordinators of each centre will supervise this process.

   Recruitment will continue until each centre has recruited the number of participants assigned by the stratification, with a 1:1 ratio. This is expected to take approximately 26 months (2 years and 2 months).

9. **Intervention:** During this period, patients will be assigned to one of the protocols for weaning, PSV in one arm of the study and ACVGV in the other.

   This process can take a few days or even a few weeks, so an extra month has been added to the projected 26 months for this stage.

10. **Follow up:** After the intervention, all patients enrolled in the study will be followed for the first 72 hours after extubation, as all clinical data will be recorded in the baby's medical record.

11. **Data registry:** As the patients are enrolled and followed up, the researchers will record the data of each variable to be studied in the data form to be later entered into a database shared by the 5 hospitals.

    This will be done by the HC or the neonatologist expert of each hospital.

Sample recruitment will take place in parallel with the intervention and follow up, as some patients will be undergoing the intervention while others are being recruited or followed up.

The newborns will be enrolled in the study while they are on invasive mechanical ventilation. Once they meet the criteria to start weaning, the intervention will start, and patients will be randomised to one of the two protocols: PSV or ACVGV. When the patient meets the criteria for extubation, the intervention is concluded, and a 72-hour follow up will begin.

While the data is registered, the data manager will be responsible for data processing, quality control and report writing for interim and final data analysis.

During this stage, three-monthly online meetings led by the principal investigator and the data manager will be held with the hospital coordinators of each participating hospital, with the aim of facilitating communication between centres, assessing compliance with deadlines, notifying problems that have occurred during this time and being able to solve them as quickly as possible.

STAGE 4: Statistical analysis and data interpretation (4 months: August – November 2026)

12. **Statistical analysis** (August – October 2026): During this period, statistical analysis of the data will be performed by a subcontracted statistician, who will analyse all the data collected by descriptive, bivariate, and multivariate analysis. He or she will be blinded to the study groups.

13. **Results and conclusions** (November 2026): The statistician will present the results to the whole research team, who will discuss the outcomes and draw conclusions.

STAGE 5: Results publication and dissemination (5 months: December 2026 – April 2027)

14. **Article writing, revision, and publication** (December – February 2027)**:** The MI will write the final article with the results and conclusions. It will be edited and supervised by English correctors and published afterwards.

15. **Dissemination** (March – April 2027)**:** The written study will be published as a journal article. National and international congresses will be attended to present the results.

10.4 Chronogram

STAGES AND ACTIVITIES	STAF	2023				2024												2025												2026												2027			
		S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A
STAGE 0 – ELABORATION OF THE PROTOCOL AND STUDY DESIGN																																													
1. First session	Main investigator Study coordinator																																												
2. Bibliographic research and protocol elaboration	Main investigator																																												
3.Contact with participating hospitals	Main investigator Study coordinator																																												
STAGE 1 – ETHICAL APPROVAL																																													
4. Ethical evaluation and approval	CEIC																																												
STAGE 2 – COORDINATION AND HEALTH PROFESSIONALS TRAINING																																													
5. First meeting with the research team	Main investigator Study coordinator Hospital coordinator																																												
6. Formation sessions	Main investigator Study coordinator Hospital coordinator Co-investigator HCP																																												
7. Creation of data base	Computer scientist																																												
STAGE 3 – SAMPLE RECRUITMENT, INTERVENTION, AND DATA COLLECTION																																													
8. Sample recruitment	Hospital coordinator Co-investigator																																												
9. Intervention																																													
10. Follow-up																																													
11. Data registry	Hospital coordinator Co-investigator Data manager																																												
STAGE 4 – STATISTICAL ANALYSIS AND DATA INTERPRETATION																																													
12. Statistical analysis	Statistical specialist																																												
13. Results and conclusions	Main investigator Study coordinator Hospital coordinator																																												
STAGE 5 – RESULTS PUBLICATION AND DISSEMINATION																																												
14. Article writing, revision and publication	Main investigator																																												
15. Dissemination	Main investigator Study coordinator																																												

11. BUDGET

11.1 Not included costs

- **Staff:** The research team personnel will not receive additional remuneration for their contributions. Economic incentives for their participation are not considered appropriate, as researchers already obtain recognition and intellectual benefits from their scientific accomplishments. They are MI, SC, HC, CI, and HCP.
- **Protocols for weaning:** as they are part of the usual clinical practice, no additional costs will be generated.
- **Insurance:** it will not be taken out, as all procedures conduced in the study are part of the usual clinical practice.

11.2 Included costs

Subcontracted services

- **Data validation and quality control:** This includes the data manager. This task will be carried out by an external company, and we estimate the cost of this service at 10.500€ (35€/h for 300 hours. A calculation of approximately one hour and a half per week have been made).
- **Statistical specialist:** Will be paid 35€/h, with an estimated total of 75 hours. The estimated budget for this service is 2.625€.
- **Computer scientist:** Will be hired to create the online database. Will be paid 30€/h, with an estimated total of 10 hours. The estimated budget for this service is 300€.

TOTAL: 10.500 + 2.625 + 300 = 13.425€

Formation costs

- **Formation sessions:** An online theorical training on neonatal resuscitation and neonatal mechanical ventilation will be offered to all professionals. The person giving the course will be paid 35€/h and will give 1 lecture of 3 hours.

TOTAL: 105€

Travel expenses, allowances, and meals costs

- **Hospital coordinators meetings:** During the study, the main investigator and the study coordinator will have one meeting with the hospital coordinators. A budget of 100€ per person has been allocated to cover travel, accommodation, and meals. There will be a total of 7 people (the 5 hospital coordinators, the main investigator, and the study coordinator).

TOTAL: 700€

Article publication and dissemination

- **Article publication:** It has an estimated cost of 2.500€. This includes the open access publication, revision, edition, formatting, layout graphic design, and preparations of the digital metadata.
- **Linguistic correction:** Before submitting the article to the journal, a linguistic proof-reader will be required to avoid errors. The estimated cost is 300€.
- **Translator:** If there is a need to translate the study in other language as Spanish, an English translator specialized in medical language may be needed. If it was necessary, the estimated cost would be about 900€.
- **National and International congress:** We must take into consideration the payment of the inscription, travels, accommodations, and diets. Two assistants, the main investigator, and the study coordinator, will assist to both of the congresses.

  The estimated cost of the national congress is 1.300€, as the registration fee is around 400 euros per person. The international congress is more expensive, so an estimation cost of 2.900€ have been done. The total budget for both congresses is about 4.200€.

TOTAL: 2.500 + 300 + 900 + 4.200 = 7.900€

TOTAL OF THE STUDY: 13.425 + 105 + 700 + 7.900 = 22.130€

Table 5 - Budget details of the study

	TYPE OF COST	UNIT COST	HOURS or UNITS	SUBTOTAL
Subcontracted services	Data validation and quality control	25€/patient	542 patients	10.500€
	Statistical specialist	35€/h	75 hours	2.625€
	Computer scientist	30€/h	10 hours	300€
				SUBTOTAL: 13.425€
Formation	Formation sessions	35€/h	3 hours	105€
				SUBTOTAL: 105€
Travel expenses, allowances, and meals costs	Hospital's coordinators meetings	100€/person	7 persons	700€
				SUBTOTAL: 700€
Article publication and dissemination	Article publication	2.500€	1	2.500€
	Linguistic correction	300€	1	300€
	Translator	900€	1	900€
	National congress	1.300€	1	1.300€
	International congress	2.900€	1	2.900€
				SUBTOTAL: 7.900€
				TOTAL: 22.130€

12. LIMITATIONS AND STRENGTHS

12.1 Limitations

There are some limitations in the protocol that need to be considered for future analysis and extrapolation of results.

Selection bias

The first potential source of bias relates to the **recruitment of the sample**. Consecutive sampling will be used, which is a non-probabilistic method. Therefore, there is a possibility of not obtaining the most representative population. In order to mitigate this selection bias and to ensure strong external validity, extensive inclusion criteria have been formulated, while exclusion criteria have been designed to reduce any confounding factors. We are aware that the sampled population may not mirror the general population. However, we consider that it is closer to the real target population that may benefit from the final results.

The second bias in the selection phase is the **participation rate**, as we assume that two years and two months of recruitment will be enough to achieve an ideal number of people to do the intervention. If this is not the case, we could extend the selection period. Another approach is to add another study centre, an option that does not pose any major challenges as the study is multicentred.

Methodological bias

The study can be an important step to prioritize one weaning protocol over the other. Although the inclusion criteria prevent the generalization of the results to all neonates, it is expected that if the results are satisfactory, a new study could be designed including neonates > 32 weeks of gestation.

It is a clinical trial that studies two different weaning protocols in preterm infants, so it is impossible to be a double-blinded design. To reduce the **detection bias**, the statistical specialist will be blinded to the participants' intervention.

Personal bias

As this is a multicentre trial, there is a potential for **performance bias**. After the child is born, a different neonatologist will attend the newborn, depending on the hospital, the day, and time of birth. This can lead these preterm newborns being treated differently regarding first minute's reanimation, a very important moment for the future outcome. To reduce this performance bias, all professionals participating in the study will recieve theoretical training in which they will all be given the same indications.

Another possible limitation, related to the fact that it is a multicentric study, is that the communication between the different hospitals must be flexible and facilitate the identification of any problems.

Confounding bias

There could be confounding factors that could affect the results. In this study, many measures have been taken to reduce this potential bias. Differences between the two groups of the clinical trial are not expected, as randomization will be used. Another preventive measure are the exclusion criteria.

Covariates have also been defined, so a multivariate analysis including these variables will be done. This will allow us to know if some of the differences found between the two groups are directly related to a confounding factor.

12. 2 Strengths

The level of **evidence** in a clinical trial is higher than in an observational study, which is where most of the complications reported in the literature come from.

Due to the nature of the study, an important strength is that **the estimated participant loss is very low**. This can be attributed to the nature of the study, as all preterm newborns on invasive mechanical ventilation require weaning. It can also be attributed to the short follow up period. This avoids or reduces the attrition bias. As it is a multicentre study, a strength is that there is an **increase in external validity**.

13. IMPACT

Newborn respiratory distress syndrome (NRDS) is the most common complication of prematurity.

The incidence of prematurity has increased over the last 50 years due to a surge in the number of established preterm births. Accordingly, the increasing number of preterm births has led to an increase in associated complications. As a result, NRDS has become more relevant in preterm infants.

Despite reductions in mortality rates, the incidence of complications and morbidity in these infants remains high, particularly in those requiring invasive mechanical ventilation, the most severe cases. Minimising the duration of this type of ventilation is essential to reduce the risk of complications, morbidity and mortality, and studies have shown that reducing the duration significantly reduces these risks.

Therefore, finding a weaning protocol that minimises the frequency of reintubations and the overall duration of weaning may reduce the associated complications and reduce morbidity and mortality from both the syndrome and mechanical ventilation.

Therefore, this research has been carried out because premature babies are an extremely vulnerable group, for whom improvements in medical care can have a significant impact on their wellbeing, both in the immediately and in the longer term.

Reducing the duration of intubation and the number of reintubations not only benefits the newborn, but also has a positive impact on the families of patients, who usually experience significant suffering during the time the baby is in the NICU, and especially while intubated.

14. FEASIBILITY

This clinical trial will take place in five hospitals, each equipped with a NICU and experienced in the treatment of preterm babies. The participation of these centres will allow the required sample size of 542 patients to be achieved within two years and two months, which is not considered a long time.

Weaning is necessary for a posterior extubation. Therefore, it is believed that parents or legal guardians will not hesitate to participate in the study, as there is no additional risk to the newborns.

The professional neonatal team of each hospital, who will be responsible for carrying out the intervention and subsequent follow-up, will be trained in the management of intubated newborns. So, they will be perfectly capable of developing the intervention of the study.

The study budget is not excessive as the necessary intervention equipment is already available in the participating hospitals. Moreover, no additional personnel will be needed except for the statistical expert, the data manager and the computer scientist.

In conclusion, this study is feasible.

15. BIBLIOGRAPHY

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16. ANNEXES

Annex 1 – APGAR score

Sign	0 points	1 point	2 points
Activity (muscle tone)	Floppy	Some tone and flexion	Active movement
Heart rate	Absent	<100 bpm	>100 bpm
Grimace (reflex irritability)	Absent	Minimal response to stimulation	Prompt response to stimulation (sneeze cough pull away)
Appearance	Blue or pale	Pink body, blue extremities	Completely pink
Respiration	Absent	Slow and irregular	Vigorous cry

Severely depressed	0-3
Moderately depressed	4-6
Excellent condition	7-10

Annex 2 - Diagnosis, signs and symptoms and treatment of NEC

Diagnosis	Signs and symptoms	Treatment strategy
Suspected NEC	Abdominal distension without radiographic evidence of pneumatosis intestinalis, portal venous gas, or free intraperitoneal air	Close clinical observation for increased abdominal distention and feeding intolerance
	Unexpected onset of feeding intolerance	Consideration of bowel decompression and brief discontinuation of feeding; abdominal radiograph; monitoring of white cell, differential, and platelet counts; consideration of blood cultures and short course of intravenous antibiotics
Definitive medial NEC	Abdominal distension with pneumatosis intestinalis, portal venous gas, or both	Bowel decompression and cessation of enteral nutrition for 7-10 days
	Other radiographic signs such as fixed, dilated bowel loops of intestine and ileus patterns are not pathognomonic but should be treated as such	Close monitoring of white cell, differential and platelet counts, blood culture and intravenous antibiotics for 7-10 days, close monitoring of abdominal radiographs, notification of surgical team
Surgical NEC	Free intraperitoneal air on abdominal radiograph after initial medical signs and symptoms	Exploratory laparotomy with resection if necessary
	Persistent ileus pattern, abdominal distention, and radiographs showing absence of bowel gas, coupled with worsening clinical and laboratory values	Placement of drain

Annex 3 – Informed consent to access into NICU

Hospital Universitari de Girona
Doctor Josep Trueta

Dades del/la pacient
Cognoms:
Nom:
NHC:

Consentiment informat

Nom del procediment:
Procediments derivats de l'Ingrés al Servei de Cures Intensives Neonatals i Pediàtriques.

Descripció del procediment:
El seu fill/a ingressa en la Unitat de Cures intensives Neonatals i Pediàtriques perquè pateix una malaltia greu, que posa en perill la seva vida, i necessita un tractament i/o vigilància especial.

Riscos generals:
Poden ser necessàries mesures o tècniques que denominem de "suport vital", que no estan lliures de riscos que vostè ha de conèixer. En el cas concret del seu fill/a li explicarem quines d'aquestes actuacions seran utilitzades i per quin motiu, sempre que la urgència ho permeti.

Riscos específics:
Aquest riscos són variables en freqüència i gravetat depenent de la tècnica i del propi pacient, però els més freqüents són:
-Els derivats de la col·locació de catèters en venes i artèries que poden donar lloc a complicacions com hemorràgies, coàguls o infecció.
-Intubació i ús de respiradors, utilitzats per ajudar a substituir la pròpia respiració, també poden tenir efectes no desitjats com infeccions pulmonars, fugida d'aire per trencament del pulmó, obturacions o lesions de la tràquea.
-Reaccions adverses, fonamentalment a medicaments, per reacció al·lèrgica o efectes secundaris.
-Toracocentesis: punció de l'espai pleural per fins diagnòstics i extracció d'aire o líquid amb fins terapèutics. Pot tenir efectes no desitjats com fugida d'aire per punció del pulmó, fugida d'aire sota la pell, hemorràgia pulmonar, lesió de vasos intercostals o lesió de les vísceres abdominals.
-Pericardiocentesis: tractament del tamponament cardíac i anàlisi del líquid extret per fins diagnòstics. Pot tenir efectes no desitjats com lesió del miocardi, punció d'una artèria coronària, arítmies, lesió del pulmó o lesió de vísceres abdominals.
Les persones que cuiden al seu fill/a coneixen aquestes possibilitats i estan atents a la seva possible aparició per combatre-les, cosa que generalment transcorre amb èxit. Tot i que els efectes secundaris poden agreujar la situació del pacient, els possibles beneficis d'aquestes mesures o tècniques superen àmpliament els riscos que comporten, és per aquest motiu que només es solen utilitzar en pacients greus.

Riscos personals:
-
-
-
-

.....pare/mare/tutor de.....
expressa que ha estat informat pel Dr/a..... del motiu pel que el meu fill/a ingressa a la Unitat de Cures intensives Neonatals i Pediàtriques, de les tècniques que poden ser necessàries aplicar-li i dels riscos que poden derivar-se de les mateixes. Comprenc el contingut d'aquest document, he rebut la informació suplementària sol·licitada i accepto les mesures necessàries. En qualsevol moment de l'evolució de la malaltia del meu fill/a podré reconsiderar aquesta decisió.

A Girona, a ..... de .....de 20.....

Signatura i DNI de/la pacient o responsable legal. Signatura del metge que informa i número de col·legiat

Annex 4 - Informed sheet to legal representatives

FULL D'INFORMACIÓ AL FAMILIAR RESPONSABLE O AL REPRESENTANT LEGAL

Nom de l'estudi: Comparació de dos protocols de weaning en prematurs de menys de 32 setmanes gestacionals amb síndrome de distrés respiratori del prematur

Centre assistencial:

Investigador principal:

Introducció

Ens dirigim a vostè per informar-lo/la sobre un estudi d'investigació al que volem que el seu fill/a o representat legal participi.

L'estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de l'Hospital Universitari Dr Josep Trueta de Girona, d'acord amb la legislació vigent, i amb respecte als principis enunciats en la declaració d'Hèlsinki i a les guies de bona pràctica clínica.

La intenció del present document és que vostè rebi la informació necessària sobre l'estudi per tal que pugui decidir si vol participar-hi, de forma completament lliure i voluntària. Li preguem que llegeixi detingudament aquest document i, en cas de sorgir-li qualsevol dubte o pregunta, es dirigeixi a l'investigador principal o als membres de l'equip de recerca per tal d'aclarir-los.

Participació voluntària

La seva participació en aquest estudi és voluntària i pot canviar la seva decisió en qualsevol moment, revocant el consentiment informat, sense necessitat de justificar-se i sense que es produeixi cap alteració en la relació amb el seu metge ni cap prejudici en la seva atenció sanitària.

Descripció de l'estudi

El weaning és un procediment que es realitza en persones que estan intubades i és el pas previ a l'extubació. Aquest procediment serveix per tal que els pacients puguin fer una transició de manera progressiva del suport ventilatori a una respiració espontània. Actualment hi ha dos protocols de weaning utilitzats a la pràctica clínica. Els dos s'ha demostrat que són eficaços i segurs pels pacients, però no està clar quin dels dos és més efectiu.

Per aquest motiu, s'ha realitzat aquest assaig clínic, per tal de comparar aquests dos protocols ja utilitzats als hospitals. El que es farà en l'estudi és assignar de manera aleatòria un dels dos protocols de weaning. Al ser aleatoritzat, tots els pacients tenen les mateixes possibilitats de fer el procés de weaning amb qualsevol dels dos protocols.

Quin és l'objectiu de l'estudi

El principal objectiu de l'estudi és comparar dos protocols de weaning (*ventilació amb pressió de suport* i *ventilació assistida controlada amb volum garantit)*. Per tal de fer-ho, es compararà el nombre de reintubacions i el temps de weaning dels dels protocols, per saber quin dels dos és el més efectiu. S'ha demostrat que una reducció del nombre de reintubacions i de temps de weaning també disminueix les complicacions posteriors associades a la malaltia.

Quants centres hi participen i quant temps dura?

En aquest estudi hi participaran una totalitat de 5 hospitals de Catalunya. Són els 5 hospitals amb major incidència de nounats prematurs de Catalunya i tots tenen UCI neonatal. Els hospitals són els següents: Hospital 1, Hospital 2, Hospital 3, Hospital 4 i Hospital 5.

L'estudi està previst que tinguin una duració de 4 anys.

Quines característiques han de reunir les pacients per participar en l'estudi?

Cal complir uns criteris per tal d'entrar a l'estudi. Cal que el nounat hagi nascut abans de les 32 setmanes de gestació i que tingui el síndrome de distrés respiratori del prematur. A més, que degut a l'evolució d'aquest síndrome, hagi requerit ventilació mecànica invasiva per al seu maneig.

També hi ha un seguit de criteris que no s'han de complir per tal de poder entrar a l'estudi. Aquests criteris són absència de malformacions congènites, cromosomopaties, cardiopaties ni malformacions neurològiques.

La participació implica riscos?

La participació en l'estudi no implica cap risc sobreafegit al fet de no participar a l'estudi, ja que els dos protocols de weaning utilitzats en aquest estudi estan aprovats i són utilitzats en la practica clínica.

Confidencialitat i tractament de dades personals

La informació recollida en aquest estudi serà introduïda en una base de dades per al seu anàlisi. Ningú, excepte el seu metge i el personal directament relacionat amb aquest estudi, coneixerà la identitat del seu fill/a, i en cap cas el seu nom apareixerà en un document públic. L'ús comercial d'aquestes dades està estrictament prohibit.

Tota la informació es guarda i gestiona de manera segura i confidencial, de conformitat amb el que estableix la Llei Orgànica 03/2018, del 5 de desembre i del Reglament (UE) 2016/679 del Parlament Europeu de 27 d'abril de 2016 de protecció de dades (RGPD).

Cada participant rebrà un numero que utilitzaran els investigadors per tractar les dades. Únicament els investigadors d'aquest estudi podran relacionar la seva identitat amb els codis. Les dades que es recullin podran compartir-se amb

investigadors d'altres centres nacionals i estrangers, amb finalitat únicament investigadora. Els investigadors d'altres centres no coneixeran dades que revelin la seva identitat.

En tot cas, vostè o el seu fill/a tenen dret a exercitar els drets d'oposició, accés, rectificació i cancel·lació, instal·lació en l'àmbit reconegut per RGPD. També pot limitar el tractament de dades que siguin incorrectes, sol·licitar una còpia o que es traslladin a un tercer (portabilitat) les dades que vostè ha facilitat per a l'estudi.

L'investigador està obligat a conservar les dades recollides per a l'estudi com a mínim fins a 25 anys després de la seva finalització. Posteriorment, l'informació personal només es conservarà pel centre per a la cura de la seva salut i per a altres fins d'investigació científica si vostè o el seu fill/a hagueessin atorgat el seu consentiment per a això, i si així ho permet la llei i els requisits ètics aplicables.

Li recordem que les dades no es poden eliminar encara que deixi de participar en l'estudi per garantir la validesa de la investigació i complir amb els deures. Així mateix, té dret a dirigir-se a l'Agència de Protecció de Dades si no quedés satisfet/a.

És obligatòria la participació?

La participació a l'estudi és completament voluntària. En el supòsit d'acceptar participar, vostè té el dret de revocar el consentiment en qualsevol moment, sense necessitat d'explicar-ne els motius i sense que això provoqui perjudicis en la seva assistència mèdica.

Difusió dels resultats

Un cop s'hagi finalitzat l'estudi, s'extrauran els resultats i s'elaboraran conclusions. Es preveu la publicació dels resultats a revistes científiques. Tot aquest procés es farà sempre respectant l'anonimat del participant. D'aquesta

manera, altres centres assistencials se'n podran beneficiar i podran implementar el protocol de weaning més eficaç en cas que així es demostri.

Compensació econòmica

Els investigadors que participen en l'estudi no reben cap tipus de benefici econòmic. La participació a l'estudi és voluntària i per tant, no serà remunerada. Tampoc li comportarà cap cost econòmic addicional a la pràctica clínica habitual.

Contacte en cas de dubtes

Pot posar-se en contacte amb l'investigador principal i els altres membres de l'equip de recerca si al llarg de l'estudi li sorgeixen nous dubtes o necessita més informació. Se li proporcionarà un document amb les dades de contacte corresponents.

Annex 5 – Informed consent document

CONSENTIMENT INFORMAT

Títol de l'estudi:

Jo _____(nom i cognoms), en qualitat de _____ (relació amb el pacient) de _____(nom i cognoms del pacient), declaro que:

- He rebut i llegit el Full Informatiu que se m'ha entregat.
- He rebut la informació suficient del membre responsable de l'equip investigador anomenat a sota, en relació a les característiques, objectius i possibles riscos de l'estudi.
- He pogut formular les preguntes que he considerat oportunes sobre l'estudi i que, aquestes han estat respostes satisfactòriament per l'investigador responsable.
- He estat informat/ada per l'investigador_____.

De conformitat amb el que estableix el Reglament (UE) 2016/679 del Parlament i del Consell, de 27 d'abril de 2016, relatiu a la protecció de les persones físiques pel que fa al tractament de dades personals i a la lliure circulació d'aquestes dades i pel qual es deroga la Directiva 95/46/CE (Reglament general de protecció de dades) (DOUE 4.5.2016), declaro haver estat informada de:

- L'existència d'una base de dades on s'inclouran les meves dades de caràcter personal
- De la finalitat de la seva recollida i dels destinataris de la informació
- Del procés de codificació de les dades
- De la disponibilitat d'exercir els drets d'accés rectificació, cancel·lació i oposició dirigint-me per escrit al titular de la base de dades

I consenteixo que les dades clíniques referents al meu embaràs i part siguin emmagatzemades en un fitxer automatitzat, la informació del qual podrà ésser utilitzada exclusivament amb finalitats científiques.

També declaro que la meva participació és voluntària i que puc retirar-me de l'estudi:

- Quan vulgui
- Sense haver de donar explicacions
- Sense que això repercuteixi en el seguiment i cures mèdiques del pacient

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

FIRMA FAMILIAR O TUTOR LEGAL	**FIRMA DE L'INVESTIGADOR**
Nom:	Nom:
Data:	Data:

Annex 6 – Withdrawn consent

REVOCACIÓ DEL CONSENTIMENT

Jo _____(nom i cognoms), en qualitat de _____ (relació amb el pacient) de _____(nom i cognoms del pacient), revoco el consentiment informat prèviament firmat de participar en l'estudi *Comparació de dos protocols de weaning en prematurs de menys de 32 setmanes gestacionals amb síndrome de distrés respiratori del prematur.*

FIRMA FAMILIAR O TUTOR LEGAL
Data:

Annex 7 – Data form

ETIQUETA IDENTIFICATIVA

DATA FORM

En relació amb el pacient

Setmanes de gestació	
Tipo de preterme	
Per al néixer	
Sexe	
CPR després de néixer	
Apgar score als 5 minuts	

En relació amb la mare

Part preterme previ	
Avortament del segon trimestre	
Edat	
Alçada	
Cirurgia cervical prèvia	
Anomalia uterina congènita	
Diabetis pregestacional	
Malaltia de transmissió sexual	
Fumadora	
Consum alcohol o altres tòxics	
Període intragestacional curt	
Infecció extrauterina	

En relació amb l'embaràs

Embaràs múltiple	
Corioamnionitis	
Ruptura prematura de membranes	
Diabetis gestacional	

En relació amb la intervenció

Codi del protocol utilitzat	
Reintubació	
Temps de weaning (en dies)	