STATEMENT OF THE PROGRAMME RETICS COORDINATOR

RETIC Code
RD16/0022/0001

Network (Thematic area):	MATERNAL, INFANT AND DEVELOPMENTAL HEALTH RESEARCH NETWORK
Programme Title:	Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.
Programme Leader:	MAXIMO VENTO TORRES
Applicant institution:	FUNDACION PARA LA INVESTIGACIÓN HOSPITAL LA FE
Work institution:	HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE
Requested budget:	2.473.100,00 €

List of PI Participants

Nº	Family Name	First Name	Work Institution	Research	Group	Nº of Members
1	VENTO TORRES	MAXIMO	HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE	Clinical	Clinical	17
2	CABAÑAS GONZÁLEZ	FERNANDO	HOSPITAL UNIVERSITARIO LA PAZ	Clinical	Clinical	16
3	PALLÁS ALONSO	CARMEN ROSA	HOSPITAL 12 DE OCTUBRE	Clinical	Clinical	18
4	GÓMEZ ROIG	DOLORES	HOSPITAL SANT JOAN DE DEU	Clinical	Clinical	11
5	LLURBA OLIVÉ	ELISA	HOSPITAL VALL D'HEBRÓN	Clinical	Clinical	7
6	LÓPEZ DE HEREDIA GOYA	JON	BIOCRUCES	Clinical	Clinical	10
7	GARCÍA ALGAR	OSCAR	HOSPITAL DEL MAR	Clinical	Clinical	10
8	LÓPEZ HERCE CID	JESÚS	HOSPITAL GREGORIO MARAÑÓN	Clinical	Research	16
9	MARTINEZ MARTINEZ	LEOPOLDO	HOSPITAL UNIVERSITARIO LA PAZ	Basic	Research	5
10	RODRIGUEZ MARTINEZ	GERARDO	HOSPITAL CLINICO UNIVERSITARIO ZARAGOZA	Clinical	Clinical	9
11	MESA GARCÍA	MARÍA DOLORES	UNIVERSIDAD DE GRANADA	Basic	Research	5
12	CABERO PÉREZ	MARÍA JESÚS	HOSPITAL MARQUÉS DE VALDECILLA	Clinical	Research	5
13	LARQUÉ DAZA	ELVIRA	UNIVERSIDAD DE MURCIA	Basic	Research	5

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

BACKGROUND

Importance and scope of the programme at national and international levels; burden of disease mortality and mobility and disability; state of the art in Spain an in the international context.

Max. 3 pages (15,700 characters)

Introduction

Environmental, nutritional, infectious conditions and other circumstances affecting the human being during evolving life from the fetus to the end of adolescence have been only recently recognize as relevant factors contributing to the pathogenesis of acute and of chronic conditions representing a substantial burden for the individual and the society in the adult life. The theory cellular programming sustains that conditions or epigenetic factors that occurr during fetal life or ulterior life may alter genetic cell expression and provoke functional/metabolic alterations that will lead to conditions such as hypertension, obesity, insulin resistance, neurocognitive deterioration, asma, etc., that undoubtedly will influence health during adult life or even the aging periods. In this scenario, perinatal mortality and morbidity have been acknolewledged among the most relevant indices of health care level. Our group aims to especially address those circumstances in the perinatal period that may influence postnatal outcome in the newborn, infancy and childhood periods.

Pregnancy mother and children mortality and complications

Although there has been a substantial improvement in the annual number of maternal deaths in the last two decades, an estimated of approximately 300.000 women die every year as a result of maternal causes. Moreover, among women who survive childbirth, approximately 10 million will suffer from complications related to pregnancy and childbirth. Many of these complications leading to long-term morbidity could be prevented through timely interventions that have proven to be successful and economically affordable. Mortality in children under the age of five has also been significantly reduced almost 50% in the last 20 years. However, neonatal mortality has not followed this successful path, and the percentage of neonatal deaths among all deaths under five deaths has even increased from 35% to 44% in 2012. Remarkably, neonatal outcomes are inevitably linked to maternal health and, therefore, to the quality of perinatal care received by pregnant women, but especially labour, delivery and the immediate postpartum period.

Pre-eclampsia

Preeclampsia remains one of the most prevalent complications of pregnancy. Recent statistics show that it may affect ~5–7% of pregnancies in the United States, and approximately 2.3% in Spain. Guidelines from the American Congress of Obstetricians and Gynecologists define a positive diagnosis with new-onset hypertension coupled with proteinuria or any of a spectrum of other symptoms: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral/visual symptoms. Although improved obstetrical care has significantly diminished preeclampsia associated maternal mortality it still remains a leading cause of peripartum mobidity, and a major cause of prematurity due to life threatening symptoms in the mother._ Risk factors that have been associated with preeclampsia include elevated BMI, primiparity, multiparity, and ethinicity._However, despite the identification of these factors, the underlying cause of the disorder remains elusive. One mechanism that has been strongly implicated as central to the maternal symptoms is defective development of the placental unit, leading to placental hypoperfusion and chronic ischemia. Remarkably, angiogenic markers have been recently incorporated into clinical practice for the screening, diagnosing, and monitoring of preeclampsia. Our group has studied abnormal angiogenesis in the placenta which determines impaired remodeling of the maternal spiral arteries and placental underperfusion that may ultimately lead to fetal growth restriction and maternal preeclampsia. The dysregulation of angiogenesis in the placenta and maternal-fetal circulation has emerged as one of the main pathophysiological features in the development of placental insufficiency and its clinical consequences.

Chorioamnionitis

Intrauterine inflammation most commonly presents as chorioamnionitis, which is defined as a bacterial (mostly) inflammation of the chorion, amnion, and placenta. Intrauterine inflammation is one of the most common antecedents of premature birth. Remarkably, the incidence of intrauterine inflammation is inversely related to gestational age. Chorioamnionitis is present in the majority of extremely preterm births (<32 weeks gestation) and 16% of preterm births at 34 weeks. Microbiological studies indicate that intrauterine inflammation is associated with approximately 25–40% of all preterm births.Chorioamnionitis may exhibit clear clinical symptoms such as fever, leukocytosis, tachycardia or uterine tenderness, and preterm rupture of membranes; however, the most common form of presentation is subclinical and is defined histologically by inflammation of the chorion, amnion, and placenta. Histological chorioamnionitis is associated with organisms considered to be of low virulence. Deliveries prior to 30 weeks of gestation are typically associated with histological chorioamnionitis. Histological diagnosis occurs after delivery and is based on a semiquantitative assessment of inflammatory cells in chorionic membranes. However, there is a great variability in the assessment criteria for the diagnosis of histological chorioamnionitis which may influence the results of studies of histological chorioamnionitis, preterm delivery, and outcomes, and especially delay diagnosis and clinical decisions upon therapy. Fetuses exposed to chorioamnionitis develop a systemic inflammatory response known as the fetal inflammatory response syndrome (FIRS) due to the contact of the fetus with infected amniotic fluid and/or inflammatory cell transfer from the uteroplacental circulation. In a recent pilot study our group has validated and studied new biomarkers of intra-amniotic-infection that significantly correlate with clinical outcomes and provides new tools for the early diagnosis of chorioamnionitis and if proven valid in adequately powered studies will substantially improve the ability of clinicians to

undertake therapeutic decisions such as antiobiotic treatment in mother and especially in preterm newborns.

Prematurity

Our country has a National Health System that includes global care during neonatal period, postneonatal period, infancy, childhood and adolescence for all our women and children. According to the latest statistics published by the WHO, UNICEF, UNFPA and the World Bank Spain occupies a privileged place in the international context with maternal mortality <20 per 100000 live births, and neonatal deaths < 4 per 1000 live births. Remarkably, in spite of this relevant and promising numbers according to the WHO Spain occupies one of the most relevant places regarding the incidence of prematurity in developed countries in Europe representing 7.7% of all livebirths, as compared to Scandinavian countries with <4%. Of note, the incidence of prematurity has increased 36% in the last 2 decades. There are many explanatory circumstances such as increased age of mothers at first pregnancy, increased number of twin pregnancies as a consequence of the use of assisted reproductive techniques, immigrations with increased adolescent pregnancies, etc. Remarkably, very preterm infants below 32 weeks gestation are at greater risk of acute complications such as respiratory distress syndrome, intraventricular hemorrhage, infections, undernutrition, bowel perforation, etc. in the acute period and longterm complications such as bronchopulmonary dysplasia, failure to adequately thrive, neurocognitive and neurosensorial impairment with visual and auditive impairment, motor problems such as cerebral palsy, and others. Recent studies performed by the Spanish Neonatal Society (SENeo) have shown an increase in the incidence of extreme prematurity (<28 weeks gestation), increased survival of these extremely low birth weight infants (ELBW) but morbidities have plateaud.

Intrauterine growth restriction (IUGR) is defined as a significant reduction in fetal growth rate resulting in birth weight in the lowest 10th percentile for gestational age (GA) occurring in 5% to 7% of all pregnancies in developed countries. IUGR is generally caused by placental insufficiency and is associated with an abnormal umbilical artery pulsatility index or blood flow on fetal ultrasound measured with Doppler ultrasound. IUGR is associated with significant neonatal and pediatric morbidity and mortality. Approximately 5% to 10% of all pregnancies complicated by IUGR result in stillbirth or neonatal death, and suboptimal fetal growth is responsible for at least 25% of all stillbirths. The most frequent ethiological factore responsible of IUGR is placental insufficiency. Placentally restricted fetuses are chronically hypoxemic and hypoglycemic and have increased blood lactate concentrations. Placental factors include multiple placental abnormalities and umbilical-placental vascular anomalies. Most infants with IUGR show an increased postnatal growth velocity with catch-up growth by 2 to 3 years; approximately 10% remain susceptible to sustained growth delay. The effects of IUGR are prolonged in time and have an enormous impact on child growth and development development. In a recent systematic review follow up of IUGR children shows an impairment in growth and development at 3 years after birth.

Hypoxic Ischemic Encephalopathy: In addition, there is a special concern with term newborn babies affected with birth asphyxia evolving to hypoxic-ischemic encephalopathy (HIE). 1-2 newborn per 1000 births will suffer from birth asphyxia representing around 400-500 per year in our country and 4000-5000 in Europe. Out of these babies around 25% may die or develop neurocognitive and sensorial problems, especially cerebral palsy. The introduction of whole body controlled hypothermia has substantially improved outcomes of mild and moderately affected babies; however, a substantial number of those severely affected still develop serious longterm complications. Therefore, different studies are being launched to try to implement the effectiveness of hypothermia with adjunct therapies such as melatonin, allopurinol, erythropoietin, etc. Enhancing the development of early predictive biomarkers accounting for damage to the brain or predicting outcomes, improving MRI diagnosis and prognosis tools, or mathematical approach to automatic diagnosis of brain electric activity with aEEG are great challenges for the present and future of Neonatology.

Gut microbiome

The human body harbors an extremely complex microbial population, which includes around 500–1,000 different species. In the perinatal period, neonates are exposed to a ample microbial diversity but also to a enormous variety of organisms such as viruses, fungi and parasites. After weaning, the infant's gut is colonized by a rapidly diversifying microbiota that leads to an adult-like pattern of intestnal flora. The composition of the neonatal microbiota is strongly influenced by perinatal factorsi. If abnormal circumstances such as prematurity occur the establishment of a normal microbiota may result in failure in the development of a balanced immune response but also have a significant impact on the intestinal mucosal barrier function and intestinal maturation, and furthermore, these changes may predispose to specific diseases later in life sin host-microbe interactions provide a signal for immune system development and maturation. The role of microbiota in preterm birth and the consequences of prematurity upon postnatal microbiome development are emerging fields of discussion. The exact mechanisms responsible for preterm birth are multifactorial and yet not completely understood. However, there is clearly a link between infection and prematurity. Moreover, the interaction of preterm infants' altered gut microbiota with an immature immunologic intestinal response triggers proinflammatory and counter-inflammatory cytokine response. These factors will influence the pattern of bacterial gut colonization characterized by a lower microbial diversity as compared to term neonates.

Acute neurological disorders in the post-neonatal period

Several etiologies (cardiac arrest, trauma, stroke, shock, infection, toxic, etc.) can cause severe neurological damage during childhood and cause significant long-term neurocognitive sequel. It is therefore essential to study the pathophysiological mechanisms (reaction of hypoxia-hyperoxia, inflammation) involved in these alterations and to evaluate diagnostic methods that allow early diagnosis of neurological damage and establish the prognosis, to develop preventive and early treatment strategies. In recent years they have raised a number of therapeutic possibilities (hypothermia, modification of ventilation or FiO2) to improve the outcome of acute brain damage in children. Given the severity and irreversibility of neurological sequel it is necessary initially to evaluate the diagnostic and therapeutic methods in children animal models before clinical evaluation. Later it is essential to develop multicenter prospective clinical studies to obtain sufficient clinical evidence.

Metabolic syndrome and Epigenetics. Metabolic syndrome encompasses a complex network of symptoms and risk factors. It is defined by the National Institutes of Health (NIH) by having at least three of the following conditions: central

obesity, elevated triglycerides, low high-density lipoprotein cholesterol, hypertension or elevated fasting plasma glucose. Although it is widely accepted that lifestyle factors such as obesity, high caloric diet, and smoking contribute to the development of metabolic syndrome by virtue of their role in diabetes and cardiovascular disease, substantial research supports the role of early life exposures in the etiology of metabolic syndrome and related disorders including obesity and type 2 diabetes (T2D).
Our programme has as a primary objective from a multidisciplinary perspective *to improve the survival and quality of life of people intervening along the lifespan that goes from the fetal stage of life to the end of growth at the end of adolescence*.
Our approach takes into consideration:
(i) adequate monitoring of pregnancy with early detection of complications such as growth retardation, pre-eclampsia, chorioamnionitis and the influence of toxic substances on the mother and fetus.
(ii) avoidance of prematurity and prematurity associated complications.
(iii) monitoring fetal-to-neonatal transition favoring a smooth transition avoiding damage to lungs, cardiovascular and brain enhancing research on neonatal resuscitation in term and preterm infants;
(iv) enhancing research related to diagnostic tools (imaging, biochemical biomarkers, electrophysiology) and therapeutic armamentarium (hypothermia, blocking oxidative stress burst, reducing hyperexcitability, treating seizures) in the diagnosis, monitoring and treatment of neurological conditions affecting newborn infants in the postneonatal period.
(v) enhancing newborn's environment implementing family centered newborn care and nutrition with own mother's milk or human milk provided by milk banks.
(vi) establishing programs of adequate surveillance of infants and scholar nutrition and development avoiding obesity and related conditions.
(vii) enhancing infants and scholar care for severe conditions.
(viii) promoting basic and clinical research in the fields of prenatal, perinatal, postnatal care including studies in animal models and randomized clinical trials.

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Max. 1 page

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PROGRAMME OBJECTIVES

Max. 1 page

OBJECTIVE 1

To study biomarkers of Intrauterine Growth Retardation, preeclampsia and chorioamnionitis capable of predicting postnatal developmental disorders related to neurocognitive development and nutritional and metabolic status.

ACHIEVABLE RESULTS

a. To establish updated guidelines and protocols for the diagnosis, obstetrical management, and postnatal management of preeclampsia, chorioamnionitis and intrauterine growth retarded (IUGR) neonates and especially prematurity.
b. To study in IUGR neonates the correlation bewteen epidemiological, environmental, socioeconomic, maternal, and fetal hemodynamic factors with neonatal neurocognitive, neurosensorial, nutritional and during infancy.
c. To store biological samples from mothers, umbilical cord, newborn and children in an *ad hoc* section of the Biobanks of the participating groups to study the biology of chorioamnionitis, preeclampsia and IUGR.

OBJECTIVE 2

To study the efficacy of clinical indicators and biomarkers to early predicting neurocognitive and developmental outcomes and identify risk factors for neurologic sequelae in children after acute neurologic injuries, and to analyze the effectiveness of diagnostic methods and prevention strategies.

ACHIEVABLE RESULTS

a. To establish clinical and biomarkers useful to predict the neurologic evolution of acute neurologic injuries
b. To evaluate the efficacy of diagnostic, prevention and treatment measures in acute neurologic injuries.
c. To develop a Biological Resources Center cohort of acute neurologic injuries
d. To develop a pediatric experimental animal educational program

OBJECTIVE 3

To study neonatal risk factors for adverse nutritional and metabolic outcomes and possible preventive nutritional strategies.

ACHIEVABLE RESULTS

a. To enhance the use of human milk in the NICU using own mother's milk and donated human milk through milk banking.
b. To analyze the quality characteristics of donated human milk after processing (pasteurization)
c. To optimize individual fortification
d. To study evolving microbiome in preterm infants under different clinical circumstances

OBJECTIVE 4

To study pre-and-postnatal environmental factors associated with neurologic, nutritional, and metabolic conditions in the perinatal and childhood periods.

ACHIEVABLE RESULTS

a. To determine the prevalence of the prenatal and postnatal exposure to specific environmental toxics and substances of abuse.
b. Neurodevelopmental follow up of prenataly exposed newborns.

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RESEARCH ACTIVITY PROGRAMME
LIST OF WORK PACKAGES

WP Nº	WP TITLE	LEAD PARTIC.Nº	LEAD PARTICIPANT FAMILY NAME	Nº OF RESEARCH.	START DATE/ EVENT	END DATE/ EVENT
1	PRENATAL RISK FACTORS FOR ABNORMAL NEONATAL AND LONG TERM OUTCOME	5	LLURBA OLIVE	20	01/01/2017	31/12/2021
2	NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENT OUTCOME	1	VENTO TORRES	20	01/01/2017	31/12/2021
3	NEONATAL RISK FACTORS FOR ADVERSE NUTRITIONAL AND METABOLIC OUTCOME	3	PALLAS ALONSO	20	01/01/2017	31/12/2021
4	POST-NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENTAL OUTCOME.	6	LOPEZ-HERCE CID	20	01/01/2017	31/12/2021
5	POST-NEONATAL: RISK FACTORS FOR NUTRITIONAL AND METABOLIC ADVERSE OUTCOME.	11	MESA GARCIA	20	01/01/2017	31/12/2021
6	EPIGENETIC, TOXIC AND ENVIRONMENTAL RISK FACTORS FOR ABNORMAL NEURODEVELOPMENTAL, NUTRITIONAL AND METABOLIC OUTCOME	7	GARCIA ALGAR	20	01/01/2017	31/12/2021

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DESCRIPTION OF THE RESEARCH ACTIVITY PROGRAMME
WORK PLAN: WORK PACKAGES (WP), DELIVERABLES AND MILESTONES

Max. 2 pages per WP (10,700 characters)

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	1	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	PRENATAL RISK FACTORS FOR ABNORMAL NEONATAL AND LONGTERM OUTCOME						
PI Family Name	LLURBA	GOMEZ	VENTO	CABAÑAS	PALLAS	LOPEZ DE HEREDIA	GARCIA ALGAR	RODRIGUEZ
Group Nº	5	4	1	2	3	6	7	10
Nº of Resarchers	7	11	17	16	18	10	10	9

OBJECTIVES

Max. 1,200 characters

1.1 To establish a protocol for the diagnosis and obstetrical management of conditions prompting preterm delivery including preeclampsia, IUGR, chorioamnionitis.
1.2 To study the interrelation between epidemiological, toxic, environmental, socio-economic variables and maternal risk factors leading to impairment of neurodevelopment.
1.3 To study the relationship between Doppler hemodynamic compromise of umbilical blood flow and alteration of neurodevelopment.
1.4 To study the interrelation between perinatal complications, postnatal adaptation and neurodevelopment.
1.5 To develop a fetal model of IUGR, to study factor affective fetal growth and test possible preventive and therapeutic strategies.

DESCRIPTION OF WORK

Where appropriate broken down into tasks. Indicate Lead partner and role of participants.

Max. 6,500 characters

In order to achieve the aims of this WP, the network will perfom the following tasks under the leadership of Dr Elisa LLurba who is an expert in preeclampsia, chorioamnionities and IUGR. Since the study has an obstetric and a neonatal component, both professional groups will work closely to achieve relevant results at a fetal and a neonatal level. The leader of the workpackage will supervise obstetric and neonatal tasks in the intelectural and clinical work that will be reflected in protocols, abstracts, peer reviewed papers.
1) To establish a protocol for diagnosis and obstetric management of preeclampsia, chorioamnionities and IUGR: this task will be put forward by the obstetrics groups (4, 5) and the obstetricians pertaining to the rest of the groups coordinated by the Lead partner.
2) Design of an electronic notebook for data collection: this essential task will be performed in conjunction with the Informatic Groups of the Research Institute of the Vall d'Hebrón Hospital. The data base will be correlational and exportable to Statistical Package for Social Sciences (SPSS) to allow statistical calculations.
3) To study the correlation between epidemiological, toxic environment, socio-economic variables and maternal risk factors with neurodevelopment. Group 10 has experience in epidemiological studies and will assume the task of analyzing epidemiological data in the electronic sheet and put forward significant correlations. The group 7 has profound expertise in the study of the effect of non-legal toxics, medication, and ambient polutants and has also de methodology for analyzing biological material in this regard using a mass spectrometry platform.
4) Study on the correlation between Doppler hemodynamic compromise with impaired neurodevelopment. This relevant task will be undertaken by the obstetric groups 4 and 5 together with the follow up clinics of the participating perinatal centers. Babies will be studied using Bayley III scales for neurocognitive development and by ophtalmologist and otorrinolaryngologist for visual and hearing impairment respectively.
5) To study the correlation between immediate perinatal complications with impaired neurodevelopment. Neonatal groups have a dilated expertise in neonatal resuscitation and postnatal adaptation of preterm and term infants. Using data acquisition systems babies will be monitored during delivery and accumulated data will be retrieved and compared with outcomes at 24 months corrected age (Baylely III composite scoring).

6) Design of a bank from blood samples of: mothers, umbilical cord, neonates and children diagnosed with IUGR. Importantly, biological samples of the recruited cohort will be collected and stored in the Biobank of the participating hospitals. This will allow validating for biomarkers of infection/inflammation, oxidative stress, vascular dysfunction, infection, or toxics.
7) Development of animal models of chorioamnionitis, IUGR or preeclampsia. The SAMID network has several groups involved in developing animal models that can contribute to the development of an models allowing to especially study alteration of vascularization and vessel reactivity associated with preeclampsia, inflammation and pathways activated by inflammation, and oxidative stress associated alterations of biological pathways. Moreover, we have experts in biochemical, mass spectrometry and biological analysis capable of validating and determining metabolites and transcription factors relevant to theses conditions.

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) Protocol for diagnosis and obstetric management of IUGR, chorioamnionites and preeclampsia.
2) Have a register that will include epidemiological, toxic, environmental, and socio-economic variables and maternal risk factors of patients enrolled in the study.
3) Have Doppler hemodynamic variables within a given period of less than 10 days after delivery in 100% of cases and controls.
4) Record of perinatal data in a substantial percentage of study population.
5) Storing of biologic material in Biobank for ulterior study: placental, cord, blood and meconium samples from mothers and newborn infants.
6) Validating biomarkers of infection, vascular reactivity and hypoxia during gestation.
6) Using the animal model for testing different treatments with clinical potential.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

In WP1, the tasks that will be undertaken will allow to implement a clinical guideline for managing risk pregnancies with IUGR, preeclampsia and fetal hypoxia. Moreover, analysis of biologic materials will contribute to validating valuable biomarkers and the animal model will contribute to increase our knowlede of the physiology and pathophysiology of severe conditions during pregnancy such as IUGR and preeclampsia.

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WORK PLAN: WORK PACKAGES (WP), DELIVERABLES AND MILESTONES

Max. 2 pages per WP (10,700 characters)

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	2	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENT OUTCOME						
PI Family Name	VENTO	CABAÑAS	PALLAS	LOPEZ DE HEREDIA	GOMEZ	RODRIGUEZ	LLURBA	
Group Nº	1	2	3	6	4	10	5	
Nº of Resarchers	17	16	18	10	11	9	7	

OBJECTIVES

Max. 1,200 characters

1. To analyse the changes in the redox status and oxidative stress in foetal to neonatal transition, the oxidative damage to lipids, neuronal membranes, nitrosative damage, inflammation and damage caused to DNA using UPLC-MS/MS tdeveloped and validated in human biofluids in term and preterm infants.
2. To study the damage to DNA and repair especially in preterm infants.
3. Metabolic changes due to fetal to neonatal transition, oxygen supplementation, hypoxia, hyperoxia, etc. or factors changing Redox status (inflammation, infection, ventilation, etc.) in term and preterm infants.
4. To study neonatal risk factor for brain injury and adverse neurodevelopment in relation to: cerebral oxygenation, transient cardiovascular instability and encephalopathy and prematurity.
5. To develop and integrate data acquisition e-system to validate the development of algorithms to be use of early biomarkers of brain and cardiovascular dysfunction.
6. To enhance the effectiveness of hypothermia in the treatment of hypoxic ischemic encephalopathy with the use of additional therapies such as topiramate or allopurinol.
7. Establish animal models of neonatal hypoxic-isquemic brain injury.

DESCRIPTION OF WORK

Where appropriate broken down into tasks. Indicate Lead partner and role of participants.

Max. 6,500 characters

In order to achieve the aims of this WP, the network will develop the following tasks under the supervision of Lead Partner of Group 1 who has a broad CV in fetal-to-neonatal transition and resuscitation studies:
1) Study of cerebral hemodynamic imaging, macro- microcirculation and oxygen delivery (Cerebral Monitoring Techniques for the prevention of brain injury of prematurity). The group 2 has participated in a multicenter European Union financed project aiming to develop a nomogram of regional oxygenation and oxygen extraction in the brain in the perinatal period in preterm infants. Moreover, this group has also widely contributed to our knowledge of hemodynamics in the postnatal period in preterm infants especially the use of drugs and the point of care ecocardiography performed by neonatologist.
2) Analysis of biomarkers involved in brain injury: Group 1 has developed and validated in recent years using stringent requirements of the FDAa broad array of biomarkers of oxidative changes induced in biomolecules such as tyrosine oxidation byproducts for assessment of protein oxidation, guanosine base oxidation for the evaluation of damage to DNA, and especially lipid peroxidation byproducts derived from the action of free radicals upon arachidonic acid, docosahexanoic acid and adrenic acid by UPLC-MS/MS and GC-MS/MS. These biomarkers clearly reflect the action of free radicals generated during reoxygenation after an asphyctic insult.
3) Development of strategies to prevent brain injury in neonatal hypoxic-ischemic encephalopathy:
3.1. Developing early predictors of acute fetal hypoxia-ischemia and indications for C-section
3.2. Improvemnt of newborn quality of survival using "gentle" management of asphyxiated newborn infants, adequate resuscitation protocols including data acquisition systems and ventilation monitoring. Group 1 is involved in randomized controlled trials in this regard and will promote the incorporation of the rest of the groups to this multicenter trials.
3.3. Development of diagnostic and therapeutic strategies for perinatal white matter damage in preterm infants. Influence of white matter damage in later neurodevelopmental outcome.
4) Animal model of hypoxic-ischemic brain damage. Together with other international centers our groups are developing animal models allowing to study molecular and genetic mechanisms of damage in hypoxia ischemia, and validating the use of

pharmacologic therapy associated to cooling to improve outcomes.
5) Development of strategies to early detect predictive imaging in MRI using advance diagnostic tools in patients with HIE and prematurity.
6) Design of electronic systems used as early markers of brain and cardiovascular damage especially continuous electrophysiological monitorization to early detect patterns of hyperexcitability/seizures and response to drugs.

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) Nomogram of oxygen saturation in the stabilization process at different gestational ages improving the present nomogram.
2) Monitoring of non invasive ventilation using Respiratory Function Monitor to guide caregivers in the delivery room.
3) Clinical guidelines for the management of cerebral oxygenation in the extremely preterm during the transitional stage of movement.
4) Score of biomarkers in the premature circulatory failure, used to direct therapeutic interventions.
4) Score adverse prognostic risk based on analysis of parameters of different integrated monitoring systems.
5) Validation of early predictive biomarkers in biofluids allowing to take clinical decisions at early stages of HIE when MRI imaging is not yet available.
6) Early biomarkers of neuroimaging in preterm infants especially addressing white matter damage (CUS, advanced MRI)
7) Pharmacokinetics, tolerability and toxicity of different experimental treatments in asphyxic neonates undergoing moderate hypothermia.
8) Testing of different treatments with clinical potential in animal models
9) Patent of electronic systems designed.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

In summary, WP2 aims
(i) to implement a clinical guideline for management of newly born infants in the delivery room avoiding hyper-or-hypoxemia, hemodynamic instability and cardiovascular instability in extremely preterm infants, IUGR newborn infants and post-asphyctic hypoxic-ischemic encephalopathy,
(ii) to enhance the interpretation of aEEG monitoring interpretation to early establish adequate seizure or hyperexcitability or response to medication;
(iii) enhance innovative MRI predictive imaging;
(iv) determine and validate biomarkers of brain damage caused by oxidative stress.
(v) to develop and validate new biomarkers of lipid peroxidation in blood, urine and CSF using UPLC-MS/MS.
(vi) research in "new biomarkers" of hypoxia and brain damage using Untarget QTOF-MS/MS
(vii) neuroimaging biomarkers that early predict white matter damage and prognosis using MRO advanced techniques

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

WORK PLAN: WORK PACKAGES (WP), DELIVERABLES AND MILESTONES

Max. 2 pages per WP (10,700 characters)

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	3	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	INTERVENTIONS IN THE NEONATAL PERIOD TO ENHANCE ADEQUATE NUTRITION AND METABOLIC OUTCOMES						
PI Family Name	PALLAS	LOPEZ DE HEREDIA	RODRIGUEZ	GOMEZ	LLURBA	CABAÑAS	VENTO
Group Nº	3	6	10	4	5	2	1
Nº of Resarchers	18	10	9	11	7	16	17

OBJECTIVES

Max. 1,200 characters

3.1. Improve neurodevelopment of premature infants by improving nutritional approach which includes:
3.1.1. Generalization of the use of own mother's milk or human donor pasteurized milk
3.1.2. Individualizing fortification
3.1.3. Enhancing the DHA as supplement of the breast milk
3.2 To study the changes experienced by the fresh and pasteurized human milk throughout the technical proccess
3.3 To study the effect of nutritional status at discharge on body composition and glucose intolerance, and on later neurodevelopment.
3.4. To study the effect of pasteurization of donor milk upon the microbiome as compared with non-pasteurized own mothers milk
3.5. To study the quality and composition of different probiotics to assess which one promotes better colonization of the gastrointestinal tract and intestinal development, growth and neurodevelopment. In order to do so microbiome will be analyzed.
3.6.To learn the effect of protein content of the diet on protein synthesis and overall synthesis of certain proteins such as albumin in critical pediatric patient in the Pediatric Intensive Care Unit.

DESCRIPTION OF WORK

Where appropriate broken down into tasks. Indicate Lead partner and role of participants.

Max. 6,500 characters

In order to achieve the related aims of this WP, the network under the PIs supervision will develop the following tasks:
1) Promote the use of own mothers milk and human donor milk in courses given to future parents during pregnancy explaining advantages for the mother and baby, and informing about the task of the milk banks in the neonatal units.
2) To study nutritional status of babies receiving different fortification approaches using randomized controlled trials in which the hospital of the network and affiliated clinical hospitals will participate with the scientific supervision of the PI.
3) To launch randomised controlled studies to evaluate the effect of dietary advice on the concentration of DHA in breast milk.
4) Description of the relationship between nutritional status at discharge and sensitivity to insulin.
5) Launch a multicenter randomized trial comparing probiotics with different compositions and dosage of probiotic with outcomes such as: (i) late onset sepsis; (ii) NEC; (iii) nutritional status; (iv) microbiome composition in very preterm infants
6) Study of the effect of diet on overall protein metabolism and on specific individual protein synthesis.
7) Establishment of nutritional losses, immunological, antioxidants factors, vitamins and microbiome composition that suffer mother's milk after HTS pasteurization and compare it to Holder pasteurization.
8) Evaluation of the effect of speed and infusion time for power management systems, and different homogenization treatments (routine, manual, ultrasonic), change in lipid content, caloric and immunoglobulins and cytokines in thawed milk.

DELIVERABLES

Brief description and date of delivery

Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:

1) Dietary survey. Relation between intake of DHA estimated by survey and longitudinal concentration of DHA. A clinical trial will be launched.
2) Relationship between insulin sensitivity and nutritional status at discharge. Study sample size estimation to evaluate the effect of nutritional status on neurodevelopment.
3) Effect of administered probiotics on intestinal colonization during the initial admission assessed by microbiome analysis. Changes in intestinal colonization of very preterm children during the following months of discharge.
4) Effect of diet on overall protein synthesis on the splanchnic sequestration of amino acids and the synthesis of specific proteins.
5) Comparative table of nutritional losses, immune factors, antioxidants and vitamins of Holder pasteurization and HTST. Clinical guideline on the HTST pasteurization process for use of donated human milk banks.
6) Clinical guideline on the management of mother's milk.
7)Design of an infusion system that incorporates a method of homogenization.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

The ultimate aim of the present workpackage is to enhance the generalization of the use of own mothers milk and/or human donor milk processed in milk banks with optimized protocols, and assess its beneficial effects studying growth and neurodevelopment in the follow up clinic
In addition, we will evaluate microbiome composition in babies with human milk and with probiotic supplementation and evaluate which composition and dosage of probiotics better influences development of a healthy of microbiome in babies at risk.
We will perform analysis of different compounds, biomarkers, etc, before and after pasteurization using different approaches to verify which is best.
We will develop a dossier of recommendations on the implementation of human milk banks following Good Laboratory Practices.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

WORK PLAN: WORK PACKAGES (WP), DELIVERABLES AND MILESTONES

Max. 2 pages per WP (10,700 characters)

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	4	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	POST-NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENTAL OUTCOME.						
PI Family Name	LOPEZ-HERCE	LOPEZ DE HEREDIA	CABERO	MARTINEZ	PALLAS	MESA	LARQUÉ
Group Nº	8	6	12	9	3	11	13
Nº of Resarchers	16	10	5	5	18	5	5

OBJECTIVES

Max. 1,200 characters

4.1 To identify populations and postnatal risk factors for major neurodevelopmental impairment and neurological disorders in childhood.
4.2. To study the usefulness of methods for early detection of risk factors and neurological disorders: Neuroimaging methods: ultrasound, CT, MRI, PET, cerebral blood flow, NIRS, EEG, Biochemical biomarkers. Maturation of circadian rhythms.
4.3. To study the efficacy of prevention and treatment methods to reduce neurological disorders,/.Oxygenation: to analyze the influence of the fraction of inspired oxygen during cardiopulmonary resuscitation and treatment of hypoxic-ischemic alterations in the development and prevention of acute neurological injury.
4.4 To develop animal models of diagnosis, prevention and treatment of neurological diseases that occur in pediatric animal models of hypoxic neurological injury, ischemic neurologic injury and cardiac arrest.
4.5. To establish the association between oxidative, inflammatory and endothelial risk factors related to aetiology of autism spectrum.
4.6. To examine the effects of nutrition and physical exercise on cognition an

DESCRIPTION OF WORK

Where appropriate broken down into tasks. Indicate Lead partner and role of participants.

Max. 6,500 characters

In order to achieve the related aims of this WP, the network will develop the following tasks: 1) Design and development of a multicenter prospective observational studies of risk factors for neurologic impairment secondary to cardiac arrest, congenital heart disease, cardiac surgery, or secondary injury in children with long-term observation and to encourage the participation in the international multicenter study on pediatric stroke and to perform the control of long-term Spanish cohort. 2) Correlation and predictive capacity of alterations in computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), cerebral blood flow, cerebral saturation measured by near-infrared spectroscopy (NIRS), electroencephalographic (EEG) abnormalities and biomarkers of neurodevelopment damage with acute neurological and long-term neurological deficits. 3) Correlation between FiO2, respiratory rate and/or PaCO2 used in cardiopulmonary resuscitation and mechanical ventilation with acute neurological and long-term neurological deficits in children. Multicenter prospective study to analyze the effect of hypothermia in the prevention of acute neurological and long term after cardiac arrest in children beyond the neonatal period. 4) Animal model of pediatric neurological injury induced by: ischemia, hypoxia and cardiac arrest. 5) Comparison of different respiratory rates and FiO2 on cerebral blood flow, cerebral saturation measured by NIRS and biomarkers of neuronal hypoxic-hyperoxic damage on randomized experimental studies of cardiac arrest, hypoxia and ischemia. 6) To develop new methodologies based on maturation of circadian rhythm of both temperature and sleep during the first 6 months of life as an useful tool for home measurements of neurodevelopment in infants under normal living conditions.7) To evaluate oxidative, inflammatory and endothelial risk factors biomarkers related to the aetiology of autisms spectrum disease in children. 8)To evaluate postnatal neurodevelopment influenced by exercise in preadolescents overweight/

obese children.

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

1) Multicenter study of neurological disorders in children with: cardiac arrest, congenital heart disease, cardiac surgery and stroke. 2) Clinical guidelines for neuroimaging studies in children at risk of acute neurological disorders: measurements of cerebral blood flow, oxygen saturation by NIRS, EEG and brain damage biomarkers in children with risk of neurological disorders. 3) Clinical guidelines for FiO2 during cardiopulmonary and respiratory rate during cardiopulmonary resuscitation.4) Multicenter study protocol of hypothermia after cardiac arrest in children, and potentially neuroprotective drugs during hypoxia-ischemia and biomarkers of neurodevelopment damage in childhood to raise future clinical studies. 5) Pediatric animal model for brain damage of different etiologies including reports of the alterations of cerebral blood flow and saturation by NIRS,and biomarkers of oxidative stress. Experimental study protocol of the influence of FiO2 in pediatric cardiac arrest. Experimental study protocol of the influence of respiratory arrest in pediatric cardiac arrest. 6) Children diagnosed autism spectrum disorder will be compared with healthy children of the same age. Plasmatic inflammatory and oxidative stress biomarkers will be assessed in order to find a possible related pathogenic mechanism. 7) Develop a 5-months exercise program and effectiveness assessed with cutting edge technology to assess cognitive performance, brain structure and function (EEG; MRI)

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

In summary, a clinical guideline will be proposed for the early management of the various disorders that can cause brain damage (stroke, cardiac surgery, infections, hypoxia ischemia, autism spectrum disorders, obesity) including validation of circadian index function with other traditional tests as potential predictor of neurodevelopment.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

WORK PLAN: WORK PACKAGES (WP), DELIVERABLES AND MILESTONES

Max. 2 pages per WP (10,700 characters)

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	5	Start Date/Start Event	01/01/2017		End Date/End Event		31/12/2021
WP TITLE	POST-NEONATAL RISK FACTORS FOR NUTRITIONAL AND METABOLIC ADVERSE OUTCOME						
PI Family Name	MESA	LARQUE	GOMEZ	LLURBA	GARCIA ALAGAR	LOPEZ-HERCE	CABERO	PALLAS
Group Nº	11	13	4	5	7	8	12	3
Nº of Resarchers	5	5	11	7	10	16	5	18

OBJECTIVES

Max. 1,200 characters

5.1 To investigate subclinical cardiovascular disease in children 8-10 years old, with perinatal developmental factors (IUGR or extreme low birth weight) that potentially influences the future risk of this disease.
5.2. To define non-invasive approaches to identify children with early changes in cardiovascular physiology that potentially affect future cardiovascular outcome, emphasizing their potential applications in childhood.
5.3 To evaluate the biological effects of early and realistic interventions in the selected population, analyzing potential changes in the defined biomarkers.
5.4 To investigate the influence of genetic variants on the development of obesity and yo evaluate the association between those genetic variants and food habits, physical activity and biomarkers of inflammation, cardiovascular diseases risk and oxidative stress.
5.5 To establish the association between nutrition and physical exercise on metabolic outcomes in overweight/obese children.

DESCRIPTION OF WORK

Where appropriate broken down into tasks. Indicate Lead partner and role of participants.

Max. 6,500 characters

In order to achieve the related aims of this WP, the network will develop the following tasks:
1) Identification and recruitment of subjects at risk for different causative factors for alterations of the metabolic and/or nutritional status in the neonatal period and follow up clinics and submitting these patients to the respective nutrition and endocrine clinics.
2) Perform Next Generation Sequencing analysis for identifying expression of genes putting patients at risk for the development of metabolic syndrome (obesity, hypertension, insulin resistance)
3) Complete the assessment retrieving personal and family history of the metabolic syndrome components.
4) Clinical examination, including clinical signs of insulin resistance and maturation status, blood pressure, and anthropometry.
5) Assessment of nutrient intakes and food habits using a standardized interview computer assisted 24h recall and Food Frequency Questionnaire.
6) Measurements of traditional biomarkers associated with insulin resistance and metabolic syndrome.
7) Measurements of biomarkers associated with insulin resistance, inflammation and cardiovascular diseases risk.
8) Measurements of parameters associated with oxidative stress and inflammation.
9) To evaluate postnatal metabolic status influenced by nutrition and exercise in preadolescents overweight/obese children Overweight children will be included in a 5-months exercise program and compared with overweight children not included in the exercise program. Body composition (including bone), glucose and lipid metabolism and blood pressure will be determined We will discern whether the regular exercise has an impact on the metabolic status of overweight preadolescents
10) Detection of cardiovascular subclinical alterations (echocardiography), potentially related with future cardiovascular diseases risk.
10) Effect of classic intervention (nutrition and physical activity) on plasma and vascular parameters.
11) Statistical analysis.
The tasks require the IPs coordination of obstetricians/neonatologist identifying a cohort of newborn with risk factors during pregnancy (e.g.: maternal obesity; hypertension; IUGR; etc..) and neonatal period (type of nutrition, amount of protein, fortification, vitamin supplementation, catch up growth). Babies at risk in the follow up clinic will fulfil a protocol designed by the IP with the experts in nutrition and endocrinology. Babies enrolled will be studied using different tools such as anthropometry, Dual-Xray-absorptiometry, metabolomics, NGS. Results will be evaluated by a panel of experts.
The cohort will be constituted by newborn babies at risk from different hospitals in the network. Each group will be responsible for recruitment of patients and fulfilling the protocol and transfer data results to the study coordinator for analysis and ellaboration of outcomes.

DELIVERABLES

Brief description and date of delivery

Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) Epidemiology of X syndrome and report on the contributing factors: maternal, genetic variants as determined by next generation sequencing in the development of obesity. Results from the case-control study.
2) Report on the relationship between genetic variants, food habits, physical activity and biomarkers of inflammation and oxidative stress upon cardiovascular diseases with special emphasis on hypertension.
3) Report on the noninvasive (echocardiography) cardiovascular measurements and its correlation within the cardiovascular diseases risk factors.
4) Strict periodical Holter control of blood pressure in patients at risk.
5) Report on the efficacy of the intervention in terms of cardiovascular diseases risk factors reduction.
6) Efficacy of physical activity on physical health outcomes: physical fitness, body composition (including bone), glucose and lipid metabolism and blood pressure

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

Our Work Package seeks to early identify patients at risk to develop metabolic syndrome in the perinatal period. The protocol of early identification will include perinatal factors affecting the mother, the fetus and the newborn. The application of the protocol will allow to establish an epidemiological frame and score for patients at risk. Concomittantly, patients at risk will be studying using genetic and metabolomic platforms, and non-invasive cardiovascular tools (ecocardiography), and monitor of insulin resistance and hypertension.
As a consequence a protocol to define and to prevent metabolic syndrome in children by the use of early biomarkers will be put foward. This protocol will be defined by consensus and based in our results.

RETIC Code	Programme Leader:

WORK PLAN: WORK PACKAGES (WP), DELIVERABLES AND MILESTONES

Max. 2 pages per WP (10,700 characters)

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	6	Start Date/Start Event	01/01/2017		End Date/End Event		31/12/2021
WP TITLE	EPIGENETIC, TOXIC AND ENVIRONMENTAL RISK FACTORS FOR ABNORMAL NEURODEVELOPMENTAL, NUTRITIONAL AND METABOLIC OUTCOME						
PI Family Name	GARCIA ALGAR	RODRIGUEZ	GOMEZ	CABAÑAS	PALLAS	VENTO	MESA	LARQUE
Group Nº	7	10	4	2	3	1	11	13
Nº of Resarchers	10	9	11	16	18	17	5	5

OBJECTIVES

Max. 1,200 characters

6.1. Development of analytical methodology to describe and validate biomarkers of prenatal and postnatal exposure to substances and drugs of abuse, drugs of prescription, persistent organic toxics and heavy metals in different alternative matrices.
6.2 To study the prevalence of prenatal and postnatal exposure these several substances on prospective and retrospective cohorts of newborn infants born in different regions of Spain, and to perform follow-up of the cohorts of prenatally exposed newborns.
6.3. To identify epigenetic changes occurring during pubertal development in overweight and obese children
6.4. To develop animal models of prenatal exposure to xenobiotics, mainly alcohol to define biomarkers of different substances (parent substances and metabolites) to which foetus, newborn, child and adolescent can be exposed

DESCRIPTION OF WORK

Where appropriate broken down into tasks. Indicate Lead partner and role of participants.

Max. 6,500 characters

In order to achieve the related aims of this WP, the network will develop the following tasks:
1) To define paediatric alternative matrices useful for the determination of biomarkers of damage, or exposure. Furthermore, to create a biobank of clinical samples.
2) To define biomarkers of different substances (parent substances and metabolites) to which foetus, newborn, child and adolescent can be exposed (alcohol, tobacco, drugs, toxics, heavy metals). These biomarkers can be used in studies of prevalence of prenatal or postnatal exposure or in studies of tissue damage due to exposure.
3) To describe and validate the analytical methodology for each biomarker in every alternative matrix.
4) To determine the prevalence of prenatal and postnatal exposure to several substances.
5) Clinical follow up of the cohorts of prenatally exposed newborns and children to several substances.
6) Research on pharmacokinetics of drugs of prescription in children (clinical trials with drugs of prescription).
7) To identify differential epigenetic changes, particularly in the patterns of DNA methylation and circulating miRNAs, in the

blood of prepubertal and pubertal children. To this end, a prospective longitudinal study will be conducted, including prepubertal overweight and obese children that will be followed up during 3 years until pubertal maturation. Results will be compared with a control group including normal-weight children metabolically healthy and correlated with inflammatory biomarkers, cardiovascular risk factors, oxidative stress status and nutritional habits.
8) To identify novel predictive factors of metabolic risk in children and to ascertain the influence of pubertal maturation on the natural course of childhood obesity and its complications.
9) Development of animals models of prenatal exposure to several substances of abuse, mainly alcohol, in order to assess neurodevelopmental deleterious effects of prenatal exposure to alcohol in a zebra fish model and to assess antioxidants as a therapeutic approach.

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) List, detection time window, analytical methodology, significance and importance, and applicability of the alternative matrices.
2) List and table of biomarkers (parent substance, metabolites) of exposure of different substances.
3) Description of the analytical methodologies and its applicability.
4) Prevalence figures of prenatal and postnatal exposure to several substances.
5) Clinical and analytical results derived from the follow up of several substances prenatal and postnatal exposure.
6) Pharmacokinetic results and prescription recommendations and indications of medicines in children.
7) Development and validation of novel predictive factor of metabolic risk to to ascertain the influence of pubertal maturation on the natural course of childhood obesity and its complications.
8) Description of animal models of prenatal exposure to several substances of abuse, mainly alcohol.
9) To assess epigenetic damage due to prenatal exposure to alcohol and its changes related to antioxidants.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

The present Work Package aims to establish a comprehensive map of toxics (legal/no legal) to which our newborn infants are exposed. In addition, our knowledge of the reality will allow to implement clinical guidelines for the identification and treatment in the perinatal period (pregnancy and newborn period) of the consequences of drug exposure of the mother and fetus. In addition, analytical methods for the identification and grading of exposure will be validated. Matrixes used will imply biofluids from the mother including breast milk, and from the babies.
Guidelines for future parents and for the Community will be developed.
Presentation of clinical practical guidelines about prevention, diagnosis, follow up and management of prenatal exposure to different substances of abuse (i.e., human milk banks, foetal alcohol spectrum disorder diagnosis and follow up, environmental neurotoxicants, etc.).

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

LIST OF DELIVERABLES

DELIV. Nº	DELIVERABLE NAME	WP Nº	LEAD PARTICIPANT FAMILY NAME	DISSEMINANTION LEVEL	DELIVERY DATE
1	Protocol for diagnosis and obstetric management of IUGR, chorioamnionitis and preeclampsia including echography, Doppler and biomarkers.	1	GOMEZ	Public	31/12/2019
2	Provide epidemiological, toxic environmental, socio-economic variables and maternal risk factors of patients enrolled in the study. Store biomaterial (placenta, cord, blood, etc.,) in Biobank for ulterior study.	1	GOMEZ	Public	31/12/2021
3	Guidelines for the management of arterial and brain oxygenation, and respiratory function in the extremely preterm during the fetal to neonatal transition and postnatal adaptation.	2	VENTO CABAÑAS	Public	31/12/2020
4	Development and validation of oxidative stress and metabolic biomarkers in the premature circulatory failure to guide therapeutic interventions.	2	VENTO CABAÑAS	Public	31/12/2018
5	Elaboration of scores of risk of impaired neurocognitive outcome based on the analysis of clinical, analytical and metabolic parameters of different integrated monitoring systems and analytical procedures.	2	VENTO CABAÑAS	Public	31/12/2019
6	Protocols of implementation of the use of own mothers milk and human donor milk in the NICU and probiotics on nutritional outcomes, NEC, late onset sepsis and microbiome composition.	3	PALLAS	Public	
7	Effect of individualized fortification and protein supplementation on overall protein synthesis and synthesis of specific proteins. Comparative table of nutritional losses, immune factors, antioxidants and vitamins of Holder pasteurization and HTST.	3	PALLAS	Public	
8	In Pediatric Intensive Care Unit Effect of protein content in parenteral nutrition upon the overall protein synthesis on the splanchnic sequestration of amino acids and the synthesis of specific proteins.	3	PALLAS	Public	
9	Multicenter study in Pediatric Intensive Care Units of a comprehensive protocol of neurological disorders in children with: cardiac arrest, congenital heart disease, cardiac surgery and stroke.	4	LOPEZ HERCE	Public	
10	Clinical Guidelines recommendation for the use and interpretation of measurements of cerebral blood flow, cerebral saturation measured by NIRS, EEG and brain damage biomarkers in children with risk of neurological disorders.	4	LOPEZ HERCE	Public	

11	Development, validation and research of pediatric animal models for ischemic neurological damage, for hypoxic neurological damage, and for cardiac arrest.	4	LOPEZ HERCE	Public	
12	Next generation sequencing, mass spectrometry metabolites, and clinical studies on the influence of genetic variants on the development of X syndrome including obesity, insulin resistance and hypertension in babies with risk factors in the perinatal period (e.g.: IUGR, extreme prematurity, mother with > BMI). Correlation with social and nutritional habits.	5	MESA	Public	
13	Efficacy of consensus guidelines including diagnosis and clinical management upon cardiovascular diseases using non invasive methods such as ecocardiography, Holter monitorization of blood pressure, diet and exercise in infancy and scholar ages in a cohort of at risk babies.	5	MESA	Public	
14	Efficacy of consensus guidelines including diagnossi and clinical management upon obesity and insulin resistance using validated metabolic stress tests and biomarkers in infancy and scholar ages in a cohort of at risk babies.	5	MESA	Public	
15	In alternative matrices (hair meconimu, blood, urine) especially suitable for newborn infants to establish a list of legal and non legal toxics to which the pregnant mother, the fetus and the newborn (breast-feeding) have been exposed, optimal detection time frame, most suitable analytical methodology (e.g.: mass spectrometry, QTOF), relevance and applicability.	6	GARCIA ALGAR	Public	
16	Development, validation and description of the most suitable analytical methodologies and its applicability; epidemiological studies to assess prevalence figures of prenatal and postnatal exposure to several substances (legal and non legal) and include a pharmacokinetic and pharmacodyamic study of common drugs prescribed to the mother during gestation.	6	GARCIA ALGAR	Public	
17	Development of animal models of prenatal exposure to several substances (zebra fish, mice, rats) and implementation of analytical methods in tissue non available in clinical setting to optimize reliability of clinically applied methods.	6	GARCIA ALGAR	Public	

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

LIST OF MILESTONES

MILESTONE Nº	MILESTONE NAME	WP Nº	DUE DATE	MEANS OF VERIFICATION
1	Clinical guideline for managing risk pregnancies with preeclampsia, IUGR, or chronic fetal hypoxia.	1	31/12/2019	Published guidelines and peer reviewed papers.
2	Optimization of stabilization during fetal to neonatal transtion of preterm infants using an individualized approach for oxygenation and ventilation, and establish ranges of normality of specific biomarkers, neuroimaging and electrophysiology parameters and complementary drugs to hypothermia in hypoxic-ischemic encephalopathy and prematurity	2	31/12/2020	Published peer reviewed papers. Guidelines published by the Spanish Neonatal Society.
3	To develop a dossier of recommendations on the generalization of the use of human milk in the NICU, relevance and interventions in the MILK BANKS following Good Laboratory Practice, and establish the optimal Probiotic and its effects upon microbiome and NEC	3	31/12/2021	Scientific and technical reports. Microbiological Information. Peer reviewed scientific papers.
4	Clinical guideline will be proposed for the early management of the various disorders that can cause brain damage.	4	31/12/2021	International Consensus Guidelines. Peer reviewed scientific papers. Available data base
5	Protocol to define and to prevent metabolic syndrome in children by the use of early biomarkers. This protocol will be defined by consensus and based in our results.	5	31/12/2021	Cohort information at 3-4 years of age after implementation of the clinical guidelines. Peer reviewed scientific papers.
6	Presentation of clinical guidelines, for example, human milk banks, and environmental toxic (legal and non legal drugs).	6	31/12/2021	Basic and clinical scientific papers. Toxicological Guidelines for the Perinatal Periods by the Health Ministry of Spain.
7				
8				

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

SCHEDULE / TIMELINE

Please provide a diagram

Max. 1 figure (jpg format)

Workpackages	SEMESTER 1	S2	S3	S4	S5	S6	S7	S8	S9	S10
1	Protocol design Electronic data sheet registry design Statistical package design		Patients' recruitment Validation of analytical and diagnostic tools Clinical and analytical interventions Intermediate data analysis Biobank sampling						Statistical data analysis Guideline dissemination in journals, congresses, workshops etic. Peer reviewed journal publications	
2	Protocol design Validation of analytical techniques for biomarkers (UPLC-MS/MS; QTOF; GC-MS/MS) Monitoring devices ranges of normality and optimizing use and data retrievement. Data acquisition system and electronic registry		Patients' recruitment Biological samples in the Biobank Analytical determinations; retrievement and storage of clinical data.						Statistical analysis Peer reviewed journal publications Presentation in International congresses International Guidelines (ILCOR) Spanish Guidelines Dissemination at international congresses	
3	Protocol design Validation of methods of pasteurization Validation of microbiome analysis Validation of Probiotic composition and dosing Validation of biomarkers		Patients' recruitment Storage of biological samples in Biobank Analytical determinations at pre-established timing Retrievement and storage of clinical and analytical data						Statistical analysis Peer reviewed journal publications Presentation at International Congresses Dissemination of Guidelines for Milk Banking and Implementation on the use of Human Milk in the NICU.	
4	Protocol design Validation of analytical methods, imaging techniques, monitoring, and clinical outcomes. Electronic data sheet registry design and validation Consensus on clinical guidelines to be applied in the study		Patients' recruitment Attainment of biological samples Retrievement of clinical variables Retrievement and assessment of image variables Storage of biosamples in the Biobank Analytical procedures at pre-established timing						Statistical analysis Peer reviewed journal publications Presentation at International Congresses Dissemination in the from of Guidelines and Protocols at International Medical Societies	
5	Protocol design Cohort validations at different institutions participating in the study Establish in conjunction with epidemiologist the aims and scope of the study. Design of data acquisition/electronic registry Feasibility NGS and metabolomic in pilot study		Patient's recruitment Attainment of biological samples Analysis with NEXT GENERATION SEQUENCING and METABOLOMICS PLATFORM Retrievement of clinical variables						Statistical analysis Peer reviewed journal publications Guidelines for prevention of Obesity during Pregnancy and for Prevention of Metabolic Syndrome in Childhood Dissemination of results at International Congresses, Workshops, etc..	
6	Epidemiology on the exposure of legal and no legal toxic substances in the perinatal period List of matrices needed to study toxics Validation of MS processing, storing and analysis, and protocol for identification of patients at risk and procedures.		Recruitment Attainment of biological samples Attainment of clinical and educational/socio-economic variables. Storing of matrices in the Biobank Analysis at pre-establish timing						Statistical analysis Peer reviewed journal publications Guidelines on risks of exposure to LEGAL an NO LEGAL toxics during pregnancy and lactation, infancy and childhood.	

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

MANAGEMENT/COORDINATION OF WORK PACKAGES

Please provide a written description. Max. 1 page

The present structure of the RED SAMID was designed to enhance intergroup exchange and distributed the tasks among the Network Coordinator (Group 1) and sub-coordinators in charge of specific responsibilities. The structure was approved in 2015 and has rendered greatly effective as proven in the activity of the network in the last 15 months. Interaction and common projects have substantially increased thus facilitating the approach to new multicenter and multidisciplinary trials with great expectancy of success.

The coordinating team will be formed by the Programme Coordinator (Network coordinator), the Assistant Manager and the Scientific Assistant to the Programme Coordinator, and will work in close connection with the Group Leaders.

The Coordinator of the Programme #1 who is also de Network Coordinator (M Vento MD PhD) is perfectly knowledgeable of the areas of expertise in clinical and methodological aspects of the Group Leaders and components of the different workpackages integrated in this programme. Moreover, the Coordinator has a vast experience in design and accomplishment of clinical trials, methodology (molecular biology and genetic and mass spectrometry platforms), and experimental studies in animal models.

The Assistant Manager to the coordinator who is at present the Manager of the Network (A Tenería) will perform all the administrative tasks related to the Programme 1.

The Scientific Assistant, will be an expert in laboratory and analytical methodology including statistical analysis. The Scientific Assistant will run the databases of the different Workpackages and supervise the correct data input, validate data, perform statistical analysis and establish priorities.

In the following years meetings will be programmed to supervise the activity of the different groups.

The Group Leader will be responsible to assigning to specific researcher specific tasks, request dead lines for results and perform local meeting to discuss the project. Moreover, each Group Leader will have direct access by an internet platform a common data base with a username and password and will introduce his/her data at the electronic registry.

Biological samples will be directed to the pre-established laboratories as specified by the Coordinator were they will be processed and ultrafreezed until analyzed.

Clinical data of the monitoring systems will also be retrieved, filtered and stored in the electronic data registry sheet.

Imaging will be supervised by top specialists assigned to the studies by the Group Leaders in each center.

Electronic communication by an email network will be constant and Whatsapp Group will be established to better communicate especially urgent matters.

Conference calls per month initially and per trimester thereafter will be necessary to discuss priorities and logistic and tecnical issues.

Semester meetings of the Group Leaders will be necessary and will be performed in Madrid.

Preliminary results will be presented at scientific conferences and early results will be sent for publications.

Therefore, the budget will need to cover expenses for travelling and publication in top journals.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

ADDED VALUE OF SCIENTIFIC COLLABORATION AMONG THE DIFFERENT RESEARCH GROUPS AND MANAGEMENT OF THE INTELLECTUAL PROPERTY

Functional structure of the programme: describe the extension of the synergies and the added value to be obtained from the cooperative structure.

Scientific relationship between the different research groups in the proposed research topics: describe the ongoing scientific collaboration between different groups of the programme on the proposed objectives.

Describe the management of the intellectual property, in terms of access rights and exploitation agreements.

Max. 2 pages (10,700 characters)

FUNCTIONAL STRUCTURE OF THE PROGRAMME

Our programme has substantially 3 different intrinsic components: (i) clinical and epidemiological; (ii) analytical; (iii) experimental. Although the latter is not on purpose extremely relevant, it is important to underscore that many groups have animal models that largely contribute to the achievement of basic knowledge that can be translated into clinical trials, and allow the validation of extremely exquisite and specific analytical methods that permit the evaluation of biomarkers not routinely employed in the clinical setting. We will comment on the two most relevant: Clinical and Analytical.

From a clinical perspective the participating groups include (i) obstetric specialists; (ii) neonatal specialists; (iii) consultant specialists such as radiologist, endocrinologist, cardiologist, pediatric surgeons, nutritionist, pharmacologist. The leading group will be the one to whom the PI of each workpackage pertains, but will work intimately with the rest of the clinical specialists. The concurrence of several clinical groups represents an extremely valuable synergy inasmuch it is possible in the following aspects:

1) to increase recruitment of mothers and infants to the requested number to confer an adequate statistical power to the studies. Having an adequate power permits perform statistical comparisons and establish reliable results to prove outcomes in the pre-established recruitment period. Our network at present represents a total of 40-50.000 deliveries per year in referral centers of our country where pregnancies and babies at risk are referred to. This numbers allow to recruit sufficient number of patients even under the normal recruitment losses present in every study.

2) The centers that participate in Programme 1 have acquired experience participating in numerous randomized controlled trials previously. As a consequence our groups are used to recruit patients, ask for inform consent, obtain-process-and adequately keep biological samples and clinical information, fulfill electronic data sheets, etc.

3) The network permits centralization of Ethics Committee evaluation of the study protocols in just one center as requested by the new law on Clinical Trials. This is a very relevant synergy that enormously accelerates a complex process, reduces costs and speeds up the ability to start recruitment.

4) An adequate storing place for imaging (especially MRI) and aEEG evaluations will be purchased in the cloud and selected specialists will have access to the evaluation and perform the final report that will be sent to the Coordinator.

5) Centralizing electronic registry of data in one center facilitates enourmously the validations of the data and the statistical analysis by the Coordinator and his Assistant to the Coordinator, and perfectly know in real time how the things are evolving in each participating center.

From an analytical perspective only specific groups in the Programme 1 have expertise in developing, validating and performing mass spectrometry analysis using the latest technology for target and untarget metabolomics such as ultraperformance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS), gas chromatography coupled to mass spectometry (GC-MS/MS) or Quadrupole time of flight mass spectrometry (QTOF-LC-MS).

Group 1 has expertise in this regard and has published very recently a series of peer reviewed papers in first line analytical journals validating most of the protocols for the determination of the most suitable metabolites / biomarkers and will centralize all the determinations in which metabolites or biomarkers of oxidative stress.

Group 7 and 11 have also develop a platform of mass spectrometry and will determine toxic substances in mother and human matrices, complete some aspects of oxidative stress such as oxidized-LDL, vitamin E, retinol, beta-carotene, Q coenzyme (by HPLC methods), as well as several enzymes related to oxidative stress (SOD, GPx, GR, Catalase). .

Thus redox status and oxidative stress derived peroxidation byproducst in DNA, lipids, and proteins will be centralized according to the Coordinator's indication in these 3 laboratories.

Group 11 has also expertise in microbiome analysis. DNA of maternal microbiome will be extracted from heces and vaginal frotis at recruitment and fetal microbiome from meconium and stools of neonates 48hrs after birth. DNa will be amplified the variable region V3-V1 from the 16S rRNA using specific oligonucleotides. The PCR product will be pyrosequenciated in the Roche/454 GS titanium technology platform (Branford, CT, USA).

Group 11 will also analyze Calprotectin in maternal feces by ELISA to determinate gut permeability. In addition, several inflammatory biomarkers such as lipopolysacharide (LPS), binding LPS protein, and several cytokines will be also quantified as a potential link between maternal dysbiosis and fetal growth defects.

Group 13 will quantify Polyamines by HPLC. Polyamines are closely linked to cell growth and differentiation.
Group 13 will study placental structure and function inmunohistochemical analyses of proteins related to cell cycle as p53 and p51, biomarkers of placental apoptosis as caspase-3, or in situ expression of arginasa, which is involved in the arginine metabolism.
From a synergistic point of view our Network allows that samples are sent to few highly specialized centers with the following advantages:
1) To specifically select centers (platforms) where samples kept in the different Biobanks will be sent to for analysis. As probably known by the reviewers, once validation of a specific analysis is performed, and the set up of the machines is done, analysis can be performed automatically in "big numbers". This enormously reduces time, and confers much greater reliability (reproducibility) to the results.
2) Highly specialization improves the quality of the determinations and confers the groups that perform them a higher standard of quality, and induces development of technical improvements.
3) The costs of the process are significantly reduced.
4) The data can be better retrieved and stored in the general data base coming from just few selective places.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

AVAILABLE RESOURCES

Indicate the available resources to carry out the programme. Max. 2 pages (10,700 characters)

1. Web Page of the SAMID NETWORK that will allow to upload to specific links data coming from patients, imaging, electrophysiology and results of analysis. The Manager of the Network is working on the implementation of the web page, and a substantial investment is being done to facilitate the Coordinator and the Sub-coordinators input of data coming from the different groups of the Network.

2. General resources of the SAMID NETWORK
The complete resources are described in the web page at www3.redsamid.net
All centers participating in the Programme 1 have:
2.1. Access to Biobank
2.2. Specific protocols to sample, process and storing biological material until stored in the Biobank (e.g. samples retrieved during the week ends or nights)
2.3. Centrifuges
2.4. Ultrafreezers
2.5. Fungible material to collect samples
2.6. Shipment facilities (dry ice, boxes, couriers)

3. Obstetric, Neonatal and Infant Services of the SAMID NETWORK
All the centers participating in the Programm 1 have resources to effectively control and monitor pregnancy (Ecography; Doppler; etc.)
Delivery room facilities with updated installations to adequately perform resuscitation following updated protocols, retrieve information from the newborn (pulse oximetry, respiratory function, basic biochemical analysis) and sampling of biomaterial for further analysis.
Obstetric and Neonatal and Pediatric Intensive Care Units endowed with updated monitoring and therapeutic systems.

4. Metabolomic platforms for target and untarget metabolomics in biofluids and tissues
Mass spectometry triple quadrupole analyzers (QqQ): UPLC-QqQ, WatersAcquity-Xevo TQ-S
Mass spectrometry quadrupole-time of flight analyzed (QToF): UPLC-QToF, WatersAcquity-Synapt
Mass spectrometry triple quadrupole (QqQ): UPLC-QqQ, Agilent 6460 y HPLC-QqQ, Waters 2795XL-QuattroMicro
Mass spectrometry triple quadrupole time of flight analyzers (QToF): HPLC-QToF, Agilent 1100, ABSciex QSTAR Elite y GC-QToF, Agilent 7200
Liquid Chromatography Agilent 2695, with UV-VIS detection (Agilent DAD 2996) or fluorescence detection (Shimadzu RF535)

5. Genomic and epigenomic platforms
Among the various groups we have access so platforms related with genomic and epigenomic diagnosis
1. Assessment of the quality of nucleic acids:
- Determination of the concentration and contaminants of nucleic acids (RNA/DNA)
- Electrophoresis
2. Arrays
- Genotyping and gene expression using arrays
- Analysis of the results of personlized arrays Illumina platform
- Global profiles of DNA methylation using arraygs in platform ISCAN (Illumina; 450K; Epic DNA methylation beadchip)
3. Sequencing
- Conventional or Sanger sequencing
- Massive sequencing
- Studies on the validation of DNA methylation using pyrosequencing.
4. Polymerase chain reaction
-Conventional PCR
- Qualitative PCR
5. Immunoprecipiation
Studies of the global profile of histone modification or of transcription factors combining immunoprecipitation of chromatin and Next Generation Sequencing.
Studies on the transcriptomic profie in real time using RNApol-ChIP-seq technique

6. Studies of the microbiome
Groups 1, 11, and 13 have the adequate microbiologic and genetic setup with the previously described methods allow to

perform qPCR, transcriptomic analysis, functional annotations, upstream regulators and signaling pathways in fecal studies. Thus, studies on microbiome can be performed to illustrate the effect of different nutrition, supplementation con probiotics, etc.

To perform these processing we have access to the following devices

- Spectrophotometer NanoDrop 2000c Thermo Scientific
- Qubit Invitrogen fluorimeter
- Qiaxcel Qiagen t Bioanalyzer 2100 Agilent
- GeneChip® Scanner 3000 7G System Affymetrix
-ViiA7 of Applied Biosystems
-Sequencing ABI Prism 3500 of Applied Biosystems
- Sequencing 454 GS Junior of Roche
-Sequencing Ion PGM Ion Proton of Life Technologies

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

IMPACT, INNOVATION, TRANSFER AND DISSEMINATION

Describe the potential impact of the programme and the expected scientific and technological contributions; detail the adequacy of the dissemination plan and the strategy for the technology transfer.

This section should include: potencial impact on health population and National Health System; clinical guidelines or other contributions to national and international standards; patents.

Max. 3 pages (15,700 characters)

1. Potential impact of research of the proposed activities.

Our project plans to bring together the major Spanish clinical research groups in obstetric and paediatric subspecialist in neonatology, nutrition, metabolism, and neurology as well as paediatric psychologist and basic researches on aspects related to Maternal and Child Health and Development within our network and beyond. We have already planned to involve clinical researches from other groups not included in our project, but that have collaborated in the past, as Associated Clinical Groups (we have 25 groups already). This will potentiate the ability to perform epidemiological studies and above all randomised clinical trials (RCT). Research efforts will be integrated through attention to standards and interoperability to leverage resources and enhance meta-analyses.

We will continue the design and conduct RCT (7 now in progress) to potentiate our capacity and disseminate our research initiatives. This process of integration, with the possibility of adding new groups funded via competitive calls for proposals, at national, European, and even at International level. In fact, most members of the network either lead or collaborate in European-funded research projects that should enhance the international impact of our network achievements. To further maximize its impact in the areas concerned, the project will try to link and collaborate on key initiatives in the field.

The establishment of our research network will facilitate active collaborations between partners and add value to their current research activities. In addition, collaborations with other research public and private partnerships will be actively pursued. It can be anticipated that we could have a catalyst effect on relevant research activities, and thereby enable closer integration of programmes in Spain and Europe.

2. Improving the health status of Spanish population.

Our project will have a positive impact on health through the provision of information leading to cause a better short- and long-term clinical outcomes for preterm and term babies, and thus on adults both this will improve health as initially sick babies recover and grow, and by reducing psychological stress and uncertainly experienced by the parents and families of such babies, as well as that of the health care professionals involved in their care. Due to research and education, the risk of serious maternal complications during pregnancy and at the time of delivery is very low in industrialised countries such as Spain. However, there is always a fear that the baby might be born with health problems, especially if it is born prematurely.

Premature birth and intrauterine growth restriction (IUGR) are among the greatest health hazards of humankind. In fact, prematurity is the single most common cause of sickness and death among newborn babies worldwide. In addition, it imposes major financial costs on the family, health care system, society, and economy. The frequency of preterm births is rising in the developed world, potentially driven by less healthy lifestyles and diets. Spain has one of the highest levels of preterm births in the EU, of about 10 IUGR also affects mortality and morbidity, and in fact sets the early basis for adult diseases, like obesity and the metabolic syndrome.

The improvement in health, learning ability and mental capacity of the Spanish population will reduce the ongoing health and welfare costs associated with these lifetime disabilities or handicaps resulting from premature birth. Apart from that actions on prevention and management of obesity in Spanish children, having one of the highest prevalence rates among European countries, should be expected to contribute to control its epidemic increase.

3. Expected scientific and technological contributions.

The previous and ongoing scientific relationship and cooperation between the Research Groups, has involved mainly but not exclusively, the study of the different aspects on two key areas on paediatric growth and development: 1) neonatal and post-neonatal risk factors for brain injury and abnormal neurodevelopment (ND) and 2) the early nutritional factors related to the latter development of the metabolic syndrome (MS) in preadolescent children.

It should be expected that results from the project will contribute in the following areas: 1) diagnosis, evaluation of risks and

prediction and prevention of adverse consequences for foetus with IGR and hypoxia; and 2) improving neurodevelopment outcome and description of early biomarkers on term neonates with hypoxic-ischemic brain damage, and premature infants with either hyperoxia or hypoxia; 3) infants and children with multi-aetiological cerebral injury, and 4) diagnosis and prevention of nutritional factors for obesity, type 2 Diabetes and the metabolic syndrome.

4. Dissemination Strategy

An effective dissemination strategy will ensure that the rationale behind the current proposal (and ultimately the results themselves) is rapidly understood by the wider community, increasing the likelihood of adoption and thus impact on the health of Spanish citizens. The dissemination efforts will be directed to all major stakeholders as general public and parents associations (the Coordinator, Valls-i-Soler has a special interest in involving parents and greater public in the research process, as well as the research community and other stakeholders)

Moreover, some partners are also involved in European and International scientific societies. So, all partners will be actively encouraged to help disseminate our findings at national and international meetings, and we anticipate arranging special sessions on the project to be linked to international conferences such as the European Society for Paediatric Research/Society of Neonatology (ESPR/ESN), European Association of Prenatal Medicine (EAPM), and other European Societies of Paediatric Subspecialties, like Intensive Care, Surgery, Metabolism….

Website www.redsamid.net. Our website will be the central source of information for parents, public in general as well as other researchers and stakeholders. In addition to general dissemination, a section of the website will also be developed to specifically engage target industry. The site will be updated frequently with information about the status of the project, interesting news and stories, six monthly newsletters and publications generated by the project.

Dissemination will involve approaches that are specific to each WP underpinned by generic approaches that apply to the whole project. WP-specific dissemination will be targeted to the relevant research community, taking account of the nature of the results to be disseminated. Dissemination is planned to run throughout the project and will devote its efforts to adequate and its results to attract the interest of different stakeholders.

Dissemination activities have consequences in terms of both financial and time expenditure. The dissemination agenda includes the design of a communication plan, the development of communication tools, and the execution of dissemination activities in order to raise awareness of the project as a whole, and specifically of its results, among different stakeholders. Coordination will focus initially on developing a communication plan for publicizing the project and its results, thereby establishing a consistent strategy for maximizing the impact and efficiency of the communication efforts. This will fully define and formalize the four basic pillars of the communication strategy: 1) Definition of the communication objectives; 2) Identification of the target audiences; 3) Description of the dissemination actions to be tackled; 4) Specific tools to be developed in order to support effective communication.

Subsequently, the communication tools identified by the communication plan will be developed as needed, keeping in mind the actions, audiences and objectives to which these tools should serve as supporting materials. The bulk of these dissemination undertakings will entail primarily, though not exclusively, scientific interactions that will include, at least:
- Publication of scientific papers. Preference will be given to the generation of publications related with the project activities and results, submitted to Spanish and mainly international scientific journals of high impact factor and citation index.
- Presentations at relevant events (Congresses, Workshops, etc.). Participation in the organization of relevant events to present the project´s approaches and results will be promoted,
- Individual presentations and meetings with key stakeholders. To raise interest and gain support of key actors in the field, such as regulatory authorities, researchers and pharmaceutical companies, individual contacts will be established as needed. This task will provide an important connection with the study of future use of the project results.

Taken together, the expected innovations summarised above will represent significant steps in various fields of current biomedical research and are of high relevance to the goals of Spanish and European Health research. Moreover, it all seems to guaranty the adequacy of the dissemination plan and the transfer of technology strategy will have a high impact on stakeholders.

Governance.

It is noteworthy that achievement of some of our objectives is subject to a number of risks. To ensure that challenges are effectively managed and mitigated risks, our work plan comprises a strong project management that will specifically include active risk-management that will specifically include, an active risk-management and performance assessment, continually reviewing the scientific progress achieved and by measuring/measure it, against the predefined goals. A governance structure with the capacity to obtain and analyse effort and output for relevance and quality, is an essential part of the proposal, and designed to both monitor activity and recommend corrective action plans to ensure that the awarded funds and any additional collaborative funding is well managed.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

EXPECTED IMPACTS SET OUT IN THE WORK PROGRAMME

Please bind each objective with its expected impact.

Programme: Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.

OBJECTIVES INCLUDED	EXPECTED IMPACTS
To study biomarkers of Intrauterine Growth Retardation, preeclampsia and chorioamnionitis capable of predicting postnatal developmental disorders related to neurocognitive development and nutritional and metabolic status.	National and International Guidelines to early diagnose and treat Preeclampsia, IUGR and chorioamnionitis. Follow up programs to study the consequences of these conditions upon neurocognitive development until school age. Further development of biomarkers and ultrasound techniques in the field of Obstetrics Improvement of survival free of major complications of IUGR infants. Scientific peer reviewed papers
To study biomarkers capable of early predicting postnatal neurocognitive and developmental outcomes and identify risk factors for an altered postnatal development in children, and establish a correlation between biomarkers and the effectiveness of diagnostic methods and prevention strategies.	New protocols for individualized preterm stabilization in the delivery room. Randomized controlled trials to enhance the effectiveness of hypothermia in hypoxic-ischemic encephatolopathy using additional strategies. Development of cot-side diagnostic and prognostic biomarkers leading to patents, spin off enterprises. Improvement of diagnostic and therapy in the clinical setting Scientific peer reviewed papers
To study neonatal risk factors for adverse nutritional and metabolic outcomes and possible preventive nutritional strategies.	Generalization of the use of human milk, milk banking, individualized fortification in preterm infants in the NICU Studies on the effectiveness of probiotic and/or DHA supplementation and pasteurization methods in the milk banks. Microbiome. Epidemiology of risk factors in mother, fetus, newborn and infants to early develop X syndrome. Protocols of nutritional and medical interventions to diagnose infants at risk, and to improve outcomes. Genetic studies to unravel genes related to the development of obesity, resistance to insulin, hypertension. Studies on the influence of the protein content in parenteral nutrition and outcomes in the PICU. Scientific peer reviewed papers.
To study pre-and-postnatal environmental factors associated with neurologic, nutritional, and metabolic conditions in the perinatal and childhood periods.	Epidemiology of exposure to legal and illegal toxics by pregnant women and offspring. Guidelines informing on the risks of exposure to legal and illegal toxic substances. Pharmacokinetics and Pharmacodynamics of commonly used drugs and abuse substances in th perinatal period Development of new diagnostic biomarkers and tools. Research on matrices capable of unravel time and intensity of exposure to legal and illegal drugs. Animal models to study the teratogenic consequences of specific legal and illegal substances. Scientific peer reviewed papers.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

SUMMARY OF THE IMPACTS INDICATORS

Please for each expected impact bind its measurement indicator.

Programme: Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.

IMPACT	INDICATOR	TYPE	EXPECTED TIME OF ACHIEVEMENT	EXPECTED OUTCOME
Guidelines for Preeclampsia	Publication of the Spanish Ministry of Health and/or Scientific Societies	Qualitative	31/12/2019	National Recommendation
Guidelines for IUGR	Publication of the Spanish Ministry of Health and/or Scientific Societies	Qualitative	31/12/2019	National Recommendation
Guidelines for Chorioamnionitis	Publications of the Spanish Ministry of Health and/or Scientific Societies	Qualitative	31/12/2019	National Recommendation
Guidelines for Resuscitation of Preterm Infants	Publication of the Spanish Neonatal Society and International Guidelines	Qualitative	31/12/2020	National and International Recommendations
Guidelines for avoidance of obesity in Childhood	Publication of the Spanish Society of Nutrition and Spanish Ministry of Health	Qualitative	31/12/2020	National Recommendations
Guideline for the use of human milk in the NICU	Publication of the Spanish Neonatal Society	Qualitative	31/12/2019	National Recommendation
Follow Up Programs	Publication of the different Obstetric and Pediatric Societies	Qualitative	31/12/2021	National Recommendation
Biomarkers predictive of various conditions associated to Programme 1	Scientific reports after observational and randomized trials	Quantitative	31/12/2012	Peer reviewed papers
Innovative changes in the study of gene expression associated with the various conditions studied in Programme 1	Scientific reports after selective observational and interventional trials	Quantitative	31/12/2021	Peer reviewed papers
Protocols of early detection and treatment of conditions putting infants and children at risk of neurological damage	Pediatric Societies Guidelines	Quantitative	31/12/2021	National Recommendations
Interventions to "normalize" microbiome	Scientific reports following multicenter randomized trials	Quantitative	31/12/2020	Peer reviewed studies
Interventions to improve hypoxic-ischemic-encephalopathy	Scientific reports of multicenter randomized trials	Quantitative	31/12/2021	Peer reviewed studies

Obesity in Spain	Epidemiological studies	Quantitative	31/12/2021	Report to the Spanish Ministry of Health to undertake strategies to reduce obesity in mothers and children
Exposure to toxics during pregnancy and lactation	Epidemiological, teratogenic, pharmacokinetic and pharmacodynamic studies	Quantitative	31/12/2021	Report to the Spanish Ministry of Health, Ministry of Agriculture, Food and Nutrition, Ministry of Industry Report to the Pharmacy Industry

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

COMMUNICATION PLAN OVERVIEW

Describe the proposed communication activities for promoting the programme and its findings.

Programme: Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.

STAKEHOLDERS OR TARGET GROUPS	ACTIVITY OR CHANNEL	PURPOSE	PARTNERS/GROUPS
Obstetric and Pediatric Societies at a National and International level	Presentation of results in congresses Peer reviewed publications Uploading files in Webpages Collaboration with Working Groups	Expand findings and improve guidelines and protocols.	National and International Societies for Obstetrics and Gynecology; Pediatrics and Pediatric subspecialties; Neonatology; Biochemistry; Genetics; Molecular Biology;
Parents Organizations	Direct Communication	Enhance their knowledge of cutting edge research that can improve outcomes in their children	All Societies related to the aims and objectives of the Programme 1
Spanish Government	Direct Communication with the different departments	Enhance cooperation at a National level and put forward National Guidelines	Different Ministries especially Health, Research Institutes, AEMPS, ISCIII, etc.
Pharmaceutic Industry	Direct contact with Communication deparments	Enhance cooperation	AEFI Farmaindustria

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

REQUESTED BUDGET

DETAILED BUDGET FOR THE PROPOSED RESEARCH PROGRAMME

GROUP Nº	1	PI SHORT NAME	VENTO
		COST (€)	JUSTIFICATION
PERSONNEL		59,000	Full time researcher to develop, validate, and perform analysis related to the different workpackages using mass spectrometry approach, and input of data in the general data base. Full time Scientific Assistant expert in laboratory and statistics to undertake control of the general data base, validation of analytical procedures and will run the databases of the different Workpackages and supervise the correct data input, validate data, perform statistical analysis and establish priorities.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		9,000	The Coordinator has to performed meetings every year with the various IPs of the Programme 1 (12) and present data at international congresses representing the Spanish Network.
TOTAL		€ 70,000	

GROUP Nº	2	PI SHORT NAME	CABAÑAS
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to help with the development of tasks specially non invasive brain oxygenation monitoring, and to develop protocols of randomized trials, retrieve data and upload them in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	3	PI SHORT NAME	PALLAS
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher for milk bank studies, to develop protocols of randomized trials, retrieve data and upload them in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	4	PI SHORT NAME	GOMEZ
GROUP Nº	4	PI SHORT NAME	
GROUP Nº	4	PI SHORT NAME	

GROUP Nº	4	PI SHORT NAME	
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher for IUGR, preeclampsia, and placental studies, to develop protocols of randomized trials, retrieve data and upload them in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	5	PI SHORT NAME	LLURBA
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop biomarkers of vascular damage, chorioamnionitis, and IUGR; to develop protocols of randomized trials, retrieve data and upload them in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	6	PI SHORT NAME	LOPEZ DE HEREDIA
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop protocols of randomized trials, retrieve data and upload them in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	7	PI SHORT NAME	GARCIA ALGAR
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop biomarkers of exposure to toxic substance, to develop protocols of randomized trials, retrieve data and upload them in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	8	PI SHORT NAME	LOPEZ-HERCE
GROUP Nº		PI SHORT NAME	
GROUP Nº		PI SHORT NAME	

GROUP Nº		PI SHORT NAME	
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop animal model experiments and to upload data in the general data base.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	9	PI SHORT NAME	Martinez
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop experimental models and contribute to the input of data in the general database.
GOOD AND SERVICES		1,500	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,000	

GROUP Nº	10	PI SHORT NAME	RODRIGUEZ
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop epidemiological data base exportable to the general data base; cooperate in randomized controlled trials and contribute to the input of data in the general database.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	11	PI SHORT NAME	MESA
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop and validate biomarkers for oxidative stress, inflammation, microbiome and nutritional studies
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	12	PI SHORT NAME	CABERO
GROUP Nº		PI SHORT NAME	
GROUP Nº		PI SHORT NAME	
GROUP Nº		PI SHORT NAME	

GROUP Nº		PI SHORT NAME	
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to develop protocols and retrieve patients and input of data base information in randomized controlled trials.
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	13	PI SHORT NAME	LARQUÉ
GROUP Nº	13	PI SHORT NAME	LARQUE
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	Full time researcher to validate biomarkers of placental function with neurodevelopment, and metabolic and nutritional status
GOOD AND SERVICES		2,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		2,000	This group needs to continuously travel to Granada because they share common laboratory techniques and have to closely cooperate.
TOTAL		€ 33,500	

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

REQUESTED BUDGET

BUDGET JUSTIFICATION

Describe the consistency between resources, capabilities and objectives. Max. 2 pages (10,700 characters)

The Programme 1 is an ambitious program that will cover relevant aspects of Maternal and Child Health as proposed by the Network SAMID in its constitution.

1. Full time researcher justification.

The most relevant component of the budget is the contract of full time technicians.
The total amounts 29.500,00 € x 14 = 413.300,00 €. (x 5 years =2.065.000,00 €)
The groups involved in the Programme 1 have important and time consuming tasks to face. However, a substantial number of these groups are constituted by clinical researchers who have to fulfill their daily clinical activities in first place and thereafter actively participate in the tasks required by the network. In our country, there is **no protected time** for clinical researchers, and their tasks have to be performed after the usual working hours.This implies that clinical researchers have only very limited time to perform some of the tasks required by the different studies.
Therefore, clinical researchers will undertake the task of designing the studies to be performed, the protocols, the electronic data sheet registry, recruit the patients and perform sampling of biological material under the leadership of the Group Leader. However, there is a need for an additional researcher fully devoted to the project.

<u>The full time researcher will:</u>
1) Organize meetings with clinical researchers and nurses in which the PI will inform on the ongoing of the research.
2) Keep continuous contact with the rest of the Groups of the Programme 1
3) Collect, process, and store samples in the Biobank
4) Ship samples to the central laboratories when requested
5) Retrieve clinical and analytical data from the recruited patients and upload them in the general data base
6) In those groups that develop new laboratory or clinical methodologies or animal models the full time researcher will contribute to the development of these aspects of the tasks assigned to his group.
7) Prepare abstracts for dissemination of results
8) Contribute to the writing of manuscripts
9) Keep pace of the adequate ongoing of the group tasks.

<u>Full time Scientific Assistant to the Coordinator of Programme 1</u>

The enormous complexity of coordinating 13 research groups with a total of approximately 120 researchers involved in complex experimental and clinical studies requires a substantial support.

The Network Manager (Aitor Tenería) is responsable for information, budget, web page, and organizing meetings, conference calls. We want to keep the Network Manager in Biocruces, and therefore the budget corresponding to Coordination should be assigned to BIOCRUCES (BARAKALDO; BILBAO).

The Scientific Assistant in close cooperation with the Network Manager (Aitor Tenería) will undertake the tasks of
Keeping pace of the ongoing activity of the 13 groups by periodic direct electronic contact, supervision of the data base inputs, analytical and sampling advising, providing groups with relevat inforamation and helping with study design, statistics, writing of abstracts and manuscripts and dissemination of achievements.

2. Good and Services.
The clinical groups will have to ship biological samples in dry ice to the central laboratories periodically. The cost of shipment is reflected in Good and Services.
At present the most relevant peer reviewed journals require the payment of fees for accepted papers to be published. The average cost is around 1000-1200 USD.
There is the possibility of having a global budget for publications or each group have an individual amount.

3. Travel Justification

The groups that integrate the Programme 1 need to gather periodically to inform on the results of their respective tasks.
In this regard at least twice a year we will hold a Scientific Meeting with oral communications and discussion of the

circumstances implied in the tasks of all the groups and perform troubleshooting, and prepare scientific communications for dissemination in the form of abstracts or manuscripts of the achievements of the Programme 1.

The groups need to travel to international meetings to present their results.

There are several groups that have a special cooperation such as Granada and Murcia and will need to frequently visit each other and therefore the group 13 has received a greater amount of money for cooperation.

The Coordinator of the study will need to frequently visit study groups and represent the network at national and international scientific meetings.

3.

RETIC Code	Programme Leader:
RD16/0022/0001	MAXIMO VENTO TORRES

ANNEXES (Text)

Max. 2 pages (10,700 characters)

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ANNEXES (Images)

Max. 1 figure (jpg format)

RETICS Call: Statement of the Programme RETICS Coodinator

Aim: describe the proposal Research Activity Programme: objectives, work plan, work packages, deliverables and milestones.

⚠ The structure of this template has been designed to ensure that the important aspects of your proposal are presented in a way that will enable experts to make an effective assessment against the evaluation criteria.

⚠ The font type and size recommended is Arial 9 points. Please respect the page limits and do not take it as a target either! It is in your interest to keep your text as concise as possible, since experts rarely view unnecessarily long documents in a positive light.

RETICS. Organizational structure

RETIC Coordinator: scientific management ot the network (RETIC), development of training programmes, and head of the dissemination and visibility of the network (RETIC).

Progamme Leader: coordination of the Research Programmes, and monitoring compliance with their objectives.

Research group: set of researchers grouped around a Principal Investigator (PI) who collaborates in the study of the thematic field of application. They should act in coordination in the development and implementation of scientific programs within the network (RETIC).

Clinical research group: set of researches directly related to the patient care activities.

Known Issues

Section 1. List of PI participants.

Research: main focus of the research activity developed by the group, values: Basic; Epidemiologycal; Clinical

Group: characterization of the research group, values: Research; Clinical

Section 11. List of Deliverables

Dissemination level: Use one of the following values: Public (publication, fully open, web); Confidential (restricted under conditions)

Section 12. List of Milestones

Means of verification: show how you will confirm that the milestone has been attained.