STATEMENT OF THE PROGRAMME RETICS COORDINATOR

RETIC Code
RD16/0022/0015

Network (Thematic area):	MATERNAL, INFANT AND DEVELOPMENTAL HEALTH RESEARCH NETWORK
Programme Title:	CARDIOVASCULAR RISK-RELATED PRENATAL FACTORS
Programme Leader:	ELISA LLURBA OLIVÉ
Applicant institution:	FUNDACIÓ INSTITUT DE RECERCA DE LA VALL D'HEBRON (VHIR)
Work institution:	HOSPITAL UNIVERSITARIO DE LA VALL D'HEBRON
Requested budget:	2.070.750 Euros

List of PI Participants

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

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

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)

Cardiovascular risk related prenatal factors.

Cardiovascular disease is the first cause of death in developed countries. 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. Abnormal angiogenesis has also been related to other obstetric and foetal conditions such as peripartum cardiomyopathy and fetal cardiac defects, opening up new challenges for our understanding of angiogenic involvement in maternal cardiovascular function and fetal cardiac development. However, the specific mechanisms underlining maternal and fetal cardiovascular programming are not well understood.
SAMID aims to especially address those circumstances in the perinatal period that may influence postnatal cardiovascular health and will produce a feasible and effective interventions package to improve maternal and children health.

Placental vascular impairment
Placenta is a key organ in the developing human life, and its impairment is known to affects maternal and children health. Pregnancy requires both vasculogenesis and angiogenesis in the foetal compartment and angiogenesis in the maternal compartment (1). Abnormal angiogenesis in the placenta determines impaired remodelling of the maternal spiral arteries and placental underperfusion that may ultimately lead to foetal growth restriction and maternal pre-eclampsia (PE) (2-4). Evidence shows that angiogenic factors are important in the regulation of placental vasculogenesis. VEGF, PlGF and Flt1 are highly expressed by invasive cytotrophoblasts. In contrast, in preeclamptic decidua, deficient expression of pro-angiogenic factors (VEGF and PlGF) and hypoxia inducible factors (HO1) triggers abnormal remodelling of spiral arteries and trophoblast invasion (Stage 1) (5). Impaired placental perfusion leads to hypoxia and oxidative damage (Stage2). Pathologic placenta induces apoptosis, inflammation and release of anti-angiogenic factors (sFlt1 and sEnd) that promote systemic endothelial dysfunction, with vasoconstriction and end-organ ischemia, that finally leads to preeclampsia sings and syntoms (Stage 3). SAMID network has the aim to get insight into the preclinical research on the molecular mechanisms that determine abnormal placentation and dysfunction in order to provide novel placental biomarkers in the diagnosis and prognosis of preeclampsia.

Preeclampsia (PE)
PE defined as a hypertension and proteinuria after 20 weeks of gestation (6) is a leading cause of maternal and neonatal morbidity and mortality worldwide. The morbidity and mortality of this condition arises from two main causes: 1) the lack of specific and sensible methods for its diagnosis and prognosis, 2) and the fact that the course of the disease is often unpredictability at its presentation and speed of progression. The majority of deaths are undoubtedly avoidable and are due to a substandard care (7, 8). Fetal morbidity and mortality increase substantially in women with pre-eclampsia; hypertension is a major cause of stillbirths (9).
It has been recently proven that the ratio of sFlt-1 to PlGF in women who presented with a clinical suspicion of preeclampsia is useful distinguishing between women in whom preeclampsia would develop and those in whom it would not (10). In addition this ratio demonstrated to be useful to discriminate among patients that would develop maternal or fetal adverse outcome. Correct identification and diagnosis of women at risk could potentially prevent all these adverse outcomes thus;

clinical experience suggests that early detection and monitoring are beneficial.

SAMID aims to provide evidence that the re-definition of pre-eclampsia as an entity caused by a placental unbalance of angiogenic and anti-angiogenic factors and its incorporation in the diagnosis and classification of the disease would improve maternal and neonatal health.

Later cardiovascular risk in women and children with preeclampsia/IUGR

The cardiovascular implications of preeclampsia do not end with the birth of the infant and placenta. Women with preeclampsia have markedly abnormal cardiac function (11-13). Multiple studies and meta-analysis confirm that women, whose pregnancy was complicated by preeclampsia (14, 15), have higher susceptibility to CVD later in life. Whether preeclampsia directly influences the development of maternal cardiovascular disease later in life, or preeclampsia uncovers a pre-existing condition remains undetermined (16). Angiogenic factors are involved in the development of atherosclerosis and show pronounced changes during acute myocardial infarction (AMI). High PlGF levels proved to be a good predictor of mortality during a 1-year follow-up of AMI, regardless of information provided by troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (17). SAMID group would provide evidence that an anti-angiogenic state could be harmful to the human heart and that this insult could contribute to increased risk for mother and children health later in life.

Angiogenic factors are pivotal identifying small fetuses with placental underperfusion and true growth restriction. However, there is a need for studies that correlate angiogenic status with cardiovascular dysfunction in intrauterine life and subsequent risk for metabolic and cardiac disease later in life. Young offspring of pregnancies complicated by IUGR/PE already have increased blood pressure and BMI (18).

SAMID group will study novel maternal and children cardiovascular risk biomarkers and to explore potential preventive strategies to help those cases at increased risk for cardiovascular and metabolic programming.

Congenital heart defects (CHD)

Abnormalities of the heart and great arteries are the most common congenital defects, accounting for approximately 20% of all stillbirths and 30% of neonatal deaths (19). Despite significant advances in the understanding of mechanisms determining heart formation, the causes of CHD in humans remain undefined in the vast majority of cases.

Evidence from animal studies showed that angiogenic factors may be implicated in cardiac morphogenesis (20-22). Abnormal angiogenesis in heart tissue of human foetuses with CHD has been demonstrated by our group, which showed increased VEGF-A and sFlt-1 expression and overproduction of proteins such as HIF-2, HO-1 and SOD1 as a result of chronic hypoxia (23). Moreover, in isolated major foetal heart defects, maternal serum PlGF levels were decreased and sFlt-1 increased throughout gestation in women carrying a foetus with isolated major heart defects. We speculated that these fetuses may have an intrinsically altered angiogenesis, leading to an abnormal formation of the heart, which may be also present in trophoblastic cells.

Prenatal factors contribute to perinatal mortality and neurodevelopment morbidity associated with CHD, the specific prenatal causes and mechanisms of insult are largely unknown. Previous studies showed that CHD have significantly reduced blood flood resistance in the brain (24, 25). Anti-angiogenic environment during foetal life could adversely impact on the adaptative capabilities of the heart and brain later in life. We believe that evaluating the relationship between CHD and placental-related complications is an important hypothesis to explore as the subject of SAMID research network. Prenatal and postnatal factors involved in the etiology of adverse neurologic outcome in children with congenital heart disease will be assessed and the development of individualized solutions by creating true individual algorithms will be provided.

Prenatal air pollution compounds and heavy metal exposure and cardiovascular disease

Air pollution exposure during early pregnancy may interfere with placental development and subsequent

oxygen and nutrient delivery to the fetus throughout pregnancy (26, 27). Air pollution is composed of a heterogeneous mixture of compounds including ozone (O3), carbon monoxide (CO), sulfur dioxide (SO2), nitrogen oxides (NOx), liquids, and particulate matter (PM). PM pollution is linked to an increased risk for hospital admission for cardiovascular and respiratory diseases, increased risk of myocardial and an increase in the rate of hospital admissions for heart failure. In addition, a recent meta-analysis identified NO2 and SO2 exposure with CHD (28). In addition, the available literature suggests that fetal and neonatal exposure to various heavy metals could affect fetal growth and organ development (29). Perinatal maternal heavy metal exposure may have detrimental effects on the mother and the fetus.

The study of air pollution's impact and heavy metals on reproductive outcomes is still a developing area of science with many important questions unanswered, but more evidence is emerging that these environment exposures in pregnancy and early childhood put children at higher risk of adverse health outcomes later in life. SAMID network will study pre-natal environment and its influence on placental dysfunction and fetal heart development and cardiovascular disease later in life.

Prenatal exposure to alcohol and other substances of abuse

The use of illicit drugs by pregnant women may cause multiple complications for both the baby and the mother (30, 31). Although placenta acts as a barrier to protect the fetus from toxic chemicals present in the mother, it has been shown that most drugs used by the mother during pregnancy cross the placenta and reach the fetus (32). These compounds may induce changes in placental morphology by altering angiogenic and endothelial factors and even alter the proper function of the placenta by modifying biochemical pathways involved in hormone synthesis. There are only a few published studies describing morphological changes in the placenta following substance misuse during pregnancy and they have controversial results (33). Therefore, SAMID would work towards providing light into the identification of mechanism (pathological, biochemical and epigenetic changes) through which drugs induce their deleterious effects in fetal development.

Our programme has as a primary objective to provide evidence of novel prediction and prevention strategies for adverse outcome in preeclampsia, intrauterine restriction, congenital heart disease and cardiovascular risk from a perspective of merging maternal and fetal conditions through the placenta function.

Our approach takes into consideration:

- Enhancing preclinical research on the molecular mechanisms that determine abnormal placentation and dysfunction in order to provide novel placental biomarkers in the diagnosis and prognosis of preeclampsia.
- Re-definition and classification of PE for early identification of women at risk for adverse outcome in a randomized clinical trial.
- Promoting basic and clinical research in the fields of prenatal and postnatal risk factors for cardiovascular risk including studies in animal models and intervention strategies to improve maternal and children health
- Obtain prediction tools (imaging, biochemical biomarkers) for adverse neurological conditions affecting children with congenital heart disease.
- Provide recommendations for public health practitioners to regulate air pollution compounds and heavy metals levels to avoid its detrimental effects in pregnancy
- To assess whether prenatal exposure to alcohol and other substances of abuse contributes to prenatal

cardiovascular programming

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PROGRAMME OBJECTIVES

Max. 1 page

OBJECTIVE 1.
TO STUDY NOVEL PLACENTAL BIOMARKERS IN THE DIAGNOSIS AND PROGNOSIS OF PREECLAMPSIA (PE).
a) To get insight into the preclinical research on the molecular mechanisms leading to abnormal placentation and cardiovascular dysfunction.
b) To determine correlation between placental apoptosis, oxidative status, inflammation, and angiogenesis with maternal serum sFlt1/PlGF to assess severity of PE.
c) To evaluate placental transfer of key nutrients that may affect cardiovascular or neurodevelopment outcomes.
d) To investigate insulin signaling in placentas of PE and its associations to fetal growth
e)To get insight into the pathologic relationship between placental impairment and abnormal neurodevelopment in fetuses with congenital heart disease

OBJECTIVE 2.
TO DETERMINE THE USEFULNESS OF NOVEL PLACENTAL BIOMARKERS (sFlt1/PlGF ratio) IN THE DIAGNOSIS AND PROGNOSIS OF PREECLAMPSIA (PE).
a) To demonstrate that the use of sFlt1/PlGF ratio for the diagnosis and classification of PE improve maternal and neonatal outcome.
b) To collect evidence that the use of sFlt-1/PlGF ratio decreases hospital stay compared to the classical definition.
c) To elaborate a clinical score for maternal-neonatal prognosis combining prenatal maternal and fetal biomarkers.
d) To establish updated guidelines and protocols for the diagnosis, classification and management of PE with the use of the sFlt1/PlGF ratio.
e) To store biological samples from mother, umbilical cord, neonates and children in an ad hoc section of the Biobanks of the participating groups to be used for WP1 and WP3.

OBJECTIVE 3.
TO STUDY NOVEL MATERNAL AND CHILDREN CARDIOVASCULAR RISK BIOMARKERS AND TO EXPLORE POTENTIAL PREVENTIVE STRATEGIES.
a) To correlate severity of PE/IUGR with cardiovascular dysfunction parameters in mothers and fetuses and its relation with anti-angiogenic factors (sFlt1, sEng).
b) To evaluate the relationship between placental biomarkers during pregnancy and the incidence of cardiovascular injury at medium-long term in women who had had PE or intrauterine growth retardation (IUGR).
c) To create and validate an animal model to study the extent of the impact of placental insufficiency in cardiovascular targets.
d) To study the application of potential preventive measures (exercise, diet and aspirin) after childbirth to improve cardiovascular future maternal and offspring health.

OBJECTIVE 4
TO STUDY PRENATAL AND POSTNATAL FACTORS INVOLVED IN THE ETIOLOGY OF ADVERSE NEUROLOGIC OUTCOME IN CHILDREN WITH CONGENITAL HEART DISEASE.
a) To describe the neurodevelopment outcome of patients with complex CHD at 24 months of age and identify a subgroup with poorer outcome
b) To evaluate the utility of fetal and postnatal (preoperative and postoperative) diagnostic techniques for early recognition of patients at risk for altered neurologic outcome
c) To develop and validate predictive algorithms of poor later neurodevelopment in CHD patients

OBJECTIVE 5.
TO STUDY PRE-NATAL ENVIRONMENT AND IT'S INFLUENCE ON PLACENTAL DYSFUNCTION AND FETAL HEART DEVELOPMENT AND CARDIOVASCULAR DISEASE LATER IN LIFE
a) To assess the association between maternal and fetal biomarkers of placental dysfunction and exposure to air pollution compounds and heavy metals (cadmium, mercury and lead) during pregnancy
b) To assess the association between heart function and structural outcomes and exposure to air pollution compounds and heavy metals during pregnancy
c) To assess the association between placental vascular, inflammation and oxidative stress biomarkers and exposure to air pollution compounds and heavy metals during pregnancy.
d) To create and validate an animal model to study the extent of the impact of air pollution compounds and heavy metals in cardiovascular targets in maternal and offspring.

OBJECTIVE 6. PRENATAL EXPOSURE TO ALCOHOL AND OTHER SUBSTANCES OF ABUSE AS AN ETIOLOGIC FACTOR OF POSTNATAL CARDIOVASCULAR DELETERIOUS EFFECTS
a)To assess the vascular placental deleterious effects of prenatal exposure to alcohol and other substances of abuse
b)To assess the association between placentalbiomarkers(vascular, inflammation and oxidative stress)and prenatal exposure to alcohol and other substances of abuse
c)To follow up children prenatally exposed to alcohol about cardiovascular risk
d)To create and validate animals models in order to study prenatal exposure to alcohol and other substances of abuse as an etiologic factor of cardiovascular deleterious effects

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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	NOVEL PLACENTAL BIOMARKERS IN THE DIAGNOSIS AND PROGNOSIS OF PREECLAMPSIA (PE).	2	VENTO TORRES	20	01/01/2017	31/12/2021
2	ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS (sFlt1/ PIGF ratio) FOR IMPROVING MATERNAL AND NEONATAL OUTCOME	1	LLURBA OLIVE	20	01/01/2017	31/12/2021
3	To study novel maternal and children cardiovascular risk biomarkers and to explore potential preventive strategies.	8	RODRIGUEZ MARTINEZ	20	01/01/2017	31/12/2021
4	Prenatal and postnatal factors involved in the etiology of adverse neurologic outcome in children with congenital heart disease	2	CABAÑAS, FERNANDO	20	01/01/2017	31/12/2021
5	PRE-NATAL ENVIRONMENT AND IT'S INFLUENCE ON PLACENTAL DYSFUNCTION AND FETAL HEART DEVELOPMENT AND CARDIOVASCULAR DISEASE LATER IN LIFE	5	GÓMEZ ROIG	20	01/01/2017	31/12/2021
6	PRENATAL EXPOSURE TO ALCOHOL AND OTHER SUBSTANCES OF ABUSE AS AN ETIOLOGIC FACTOR OF POSTNATAL CARDIOVASCULAR DELETERIOUS EFFECTS	6	GARCÍA 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	NOVEL PLACENTAL BIOMARKERS IN THE DIAGNOSIS AND PROGNOSIS OF PREECLAMPSIA (PE).							
PI Family Name	VENTO	LLURBA	GÓMEZ	LARQUÉ	MESA			
Group Nº	2	1	5	9	11			
Nº of Resarchers	17	12	11	5	5			

OBJECTIVES

Max. 1,200 characters

OBJECTIVE 1
- To get insight into the preclinical research on the molecular mechanisms leading to abnormal placentation and cardiovascular dysfunction.
- To determine correlation between placental apoptosis, oxidative status, inflammation, and angiogenesis with maternal serum sFlt1/PlGF to assess severity of PE.
- To evaluate placental transfer of key nutrients that may affect cardiovascular or neurodevelopment outcomes.
- To investigate insulin signaling in placentas of PE and its associations to fetal growth
-To get insight into the pathologic relationship between placental impairment and abnormal neurodevelopment in fetuses with congenital heart disease

DESCRIPTION OF WORK

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

Max. 6,500 characters

Inadequate trophoblastic invasion enhances the risk for preeclampsia and growth restriction. Under these circumstances not only maternal-fetal blood flow but also to materno-fetal transfer of key nutrients may be altered thus promoting fetal programming of metabolic cardiovascular disease in the adult life. The network under the PIs supervision will develop the following task:
1.1 Harmonization of interdisciplinary research activity (Vento, Llurba, Gomez, Larque, Mesa)
1.2 Assessment of placental expression of biomarkers of placental dysfunction: Placental expression of arginine metabolism, inflammatory, oxidative status and placental apoptosis would be evaluated according to the severity of PE (Vento)
1.3 Evaluation of sFlt1/PlGF ratio in maternal and cord blood in relation to placental dysfunction: Correlation between placental apoptosis, inflammatory, oxidative status, angiogenic expression and maternal serum and cord blood sFlt1/ PlGFratio would be analysed (Llurba/Vento/Gómez).
1.4 Evaluation of insulin signaling in placenta according to different types of IUGR: Insulin signaling in placentas of PE with different types of fetal growth restriction would be studied (Mesa/Larque)
1.5 Evaluation of placental levels of fatty acid carrier MFSD2a: fatty acid carrier MFSD2a which is related to the preferential transfer of the key nutrient omega-3 fatty acid docosahexanoic (DHA) across the placenta would be investigated in relation to the severity of the disease (Larque)
1.6 Analysis of angiogenic and hypoxia expression markers in placenta from CHD: The expression of angiogenic and antiangiogenic factors together with hypoxic markers would be assessed in placental and brain tissue of fetuses with congenital heart disease undergoing termination of pregnancy (Llurba, Gómez)
1.7 Data analysis (Vento, Llurba, Gomez, Larque, Mesa)
1.8 Preparation for biomarkers patens and future industry interests and spin off (Vento, Llurba, Gomez, Larque, Mesa)
1.9 Preparation for any future interventional studies (Vento, Llurba, Gomez, Larque, Mesa)
1.10 Dissemination activities (Vento, Llurba, Gomez, Larque, Mesa)

DELIVERABLES

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

After reaching these tasks, the following outputs will be obtained:
1) To identify the relevance of placental metabolic pathways related to apoptosis, inflammation, oxidative stress and angiogenesis according to the type of PE
2) The identification of pathological pathways contributing to anti-angiogenic status in PE to generate potential therapeutic targets
3) The evaluation of placental levels of fatty acid carrier MFSD2a in PE would arise possible preventive strategies to counteract fetal growth restriction in these cases
4) The evaluation Insulin signaling in placenta from PE would arise possible preventive strategies to counteract fetal growth restriction
5) The relation between abnormal placental and brain angiogenesis in CHD fetuses would demonstrate the influence of prenatal mechanisms leading to poorer neurodevelopment in these children and open a window for prediction and prevention strategies

MILESTONES

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

In summary, an overview of the pathogenic mechanism leading to placental insufficiency according to its manifestations would be obtained to generate future hypothesis for target prevention and therapeutic interventions

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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	ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS (sFlt1/PlGF ratio) FOR IMPROVING MATERNAL AND NEONATAL OUTCOME						
PI Family Name	LLURBA	VENTO	CABAÑAS	PALLÁS	GÓMEZ	GARCÍA	LÓPEZ-HERCE	RODRÍGUEZ
Group Nº	1	2	3	4	5	6	7	8
Nº of Resarchers	12	17	16	18	11	10	16	9

OBJECTIVES

Max. 1,200 characters

To determine the usefulness of novel placental biomarkers (sFlt1/PlGF ratio) in the diagnosis and prognosis of preeclampsia (PE).
1. To demonstrate that the use of sFlt1/PlGF ratio for the diagnosis and classification of PE improve maternal and neonatal outcome.
2. To collect evidence that the use of sFlt-1/PlGF ratio decreases hospital stay compared to the classical definition.
3. To elaborate a clinical score for maternal-neonatal prognosis combining prenatal maternal and fetal biomarkers.
4. To establish updated guidelines and protocols for the diagnosis, classification and management of PE with the use of the sFlt1/PlGF ratio.
5. To store biological samples from mother, umbilical cord, neonates and children in an ad hoc section of the Biobanks of the participating groups to be used for WP1 and WP3.

DESCRIPTION OF WORK

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

Max. 6,500 characters

Since the study has an obstetric and a neonatal component, both professional obstetricians and neonatologist groups will work closely to achieve relevant results at a maternal and a neonatal level. The leader of the workpackage will supervise obstetric and neonatal tasks in the intellectual and clinical work that will be reflected in protocols, abstracts, peer reviewed papers. In order to achieve the aims of this WP, the network will perform the following tasks under the leadership of Dr Elisa LLurba:
2.1 Harmonization of interdisciplinary research activity (Llurba)
2.3 Training/education of study personnel and quality control (Llurba)
2.4 Preparation documents for Ethical Committees approval (LLurba)
2.5 Enrollement into RCT for incorporation sFlt1/PlGF ratio in the definition and management of PE (All) : an open, multicentre, national, randomized controlled trial will be carried out to demonstrate that the use of sFlt1/PlGF ratio in the diagnosis and classification of PE improves perinatal outcome. Obstetric and neonatal investigators from Clinical Groups will participate in this clinical trial. The study has a pragmatic approach aiming to reflect real clinical practice rather than the very tightly controlled circumstances of explanatory trials. Women with suspicion of the disease or with established PE will be randomly allocated in the ratio group or in the control Lopez-Herce, Rodríguezgroup. In the intervention group women with a sFlt1/PlGF ratio > 85 will be considered as having the condition irrespectively of the presence of hypertension or proteinuria. Moreover, women with PE and a ratio >210 will be considered as having severe PE. The management protocol will be applied accordingly. In addition, women with PE and a sFlt1/PlGF ratio >600 will be considered to have an immediate risk for life-threatening condition and will be offered delivery.
2.6 Biological samples from women, umbilical cord, neonates and children will be stored in the Biobank (All).
2.7 Statistical analysis (All)
2.8 A cost-effective analysis based on hospital stay after the implementation of sFlt-1/PlGF ratio will be performed (Llurba).
2.9 Clinical score for maternal-neonatal prognosis combining prenatal maternal and fetal markers will be obtained in conjunction with the Bioinformatic Group of the Research Institute of the Vall d'Hebrón Hospital (Llurba)
2.10 Guidelines and protocols for the diagnosis, classification and management of PE (All)
2.11 Preparation for biomarkers patens and future industry interests and spin off (All)

2.12 Preparation for any future interventional studies (All)

DELIVERABLES

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

After reaching these tasks, the following outputs will be obtained:
1) To reduce maternal and neonatal mortality-morbidity rate a 15%
2) Cost-effectiveness analysis of introduction sFlt1/PlGF ratio in the clinical practice
3) Clinical score for adverse outcome in preeclampsia
4) Feasible and effective interventions package to improve maternal and newborn health in women with PE
5) Storing of biologic material in Biobank for ulterior study

MILESTONES

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

To ascertain the utility of the incorporating of sFlt1/PlGF ratio in the diagnosis and management of PE in order to change polices and improve maternal and neonatal health.

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

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	To study novel maternal and children cardiovascular risk biomarkers and to explore potential preventive strategies.							
PI Family Name	RODRÍGUEZ	VENTO	GÓMEZ	LLURBA	LARQUÉ			
Group Nº	10	2	5	1	9			
Nº of Resarchers	9	17	11	12	5			

OBJECTIVES

Max. 1,200 characters

1. To correlate severity of PE/IUGR with cardiovascular dysfunction parameters in mothers and fetuses and its relation with anti-angiogenic factors (sFlt1, sEng).

2. To evaluate the relationship between placental biomarkers during pregnancy and the incidence of cardiovascular injury at medium-long term in women who had had PE or intrauterine growth retardation (IUGR).

3. To create and validate an animal model to study the extent of the impact of placental insufficiency in cardiovascular targets.

4. To study the application of potential preventive measures (exercise, diet and aspirin) after childbirth to improve cardiovascular future maternal and offspring health.

DESCRIPTION OF WORK

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

Max. 6,500 characters

Dr Rodríguez is an expert in the field of metabolic and cardiovascular disease in young children and adolescents. In order to achieve the related aims of this WP, the network will develop the following tasks:

3.1 Harmonization of interdisciplinary research activity (Rodríguez, Llurba)
3.2 Preparation documents for Ethical Committees approval (Rodríguez, Llurba)
3.3 Patient enrollment into the study (All): Maternal cardiovascular assessment: 60 women who developed PE/IUGR during pregnancy 5 to 10 years ago and 30 controls will be evaluated for cardiovascular risk markers (blood pressure, BMI, NT-proBNP, troponin, lipid profile, ADMA, inflammatory and oxidative stress markers, echocardiographic parameters, aortic intima thickness) and their cardiovascular state will be related with prenatal markers of placental and endothelial dysfunction that were collected at the time of pregnancy.
3.4 Children cardiovascular assessment (All): 60 children whose mothers developed PE/IUGR during pregnancy 5 to 10 years ago and 30 controls will be evaluated for cardiovascular risk markers (blood pressure, BMI, NT-proBNP, troponin, lipid profile, ADMA, inflammatory and oxidative stress markers, echocardiographic parameters, aortic intima thickness) and their cardiovascular state will be related with prenatal markers of placental and endothelial dysfunction that were collected at the time of pregnancy.
3.5 Laboratory analysis of samples and biobank store (All): maternal and cord blood circulating anti-angiogenic factors (sFlt-1 and sEng) levels with biomarkers of endothelial (ADMA) and cardiovascular dysfunction (NT-proBNP, troponin), echocardiographic parameters and aortic intima thickness in 50 women affected by PE/IUGR and their fetuses and neonatales.
3.6 Creation and validation animal model for preeclampsia (All): An animal model of PE (rats) will be validated using injection of adenoviruses (Ad sFlt-1). Measurements of MBP (mean blood pressure), sFlt-1 and protein in urine during pregnancy will be related to cardiovascular risk status after 6 and 12 months (blood pressure, BMI, NT-proBNP, troponin, lipid profile, inflammatory and oxidative stress markers, echocardiographic parameters, aortic intima thickness) in 30 animals and their

offprings.
3.7 Testing of preventive measures in the animal model (All) : In the animal model, different preventive measures will be applied: i) low training using rodent treadmill twice a week; ii) feeding animals with low salt diet 0.03% or iii) administration of a low dose of aspirin (5mg/Kg/day) once a week, in order to known the effects on cardiovascular health. Animal sample size will be 110 between cases and controls
3.8 Statistical analysis (All)
3.9 Guidelines and protocols for prevention of cardiovascular disease in women and children after PE/IUGR(All)
3.10 Preparation for biomarkers patens and future industry interests and spin off (All)
3.11 Preparation for any future interventional studies (All)

DELIVERABLES

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

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

1. To establish correlation between the severity of cardiovascular dysfunction and angiogenic and anti-angiogenic factors in women and fetuses affected by PE/IUGR.
2. To obtain a prenatal predictive algorithm for long-term cardiovascular maternal and foetal programme.
3. Creation and validation of an animal model of PE using injection of adenoviruses (Ad sFlt-1) to study the extent of the impact of placental insufficiency in cardiovascular targets.
4. Preventive measures after childbirth to improve cardiovascular maternal and offspring health.

MILESTONES

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

This WP will provide the information of the relevance of prenatal biomarkers to identify mother and children at risk for cardiovascular disease later in life. The creation and use of an animal model of PE will give the opportunity to develop target strategies to improve cardiovascular health.

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

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	Prenatal and postnatal factors involved in the etiology of adverse neurologic outcome in children with congenital heart disease						
PI Family Name	CABAÑAS	VENTO	PALLÁS	GÓMEZ	LLURBA	LÓPEZ-HERCE	LÓPEZ DE HEREDIA
Group Nº	3	2	4	5	1	7	10
Nº of Resarchers	17	17	18	11	12	16	10

OBJECTIVES

Max. 1,200 characters

1. To describe the neurodevelopment outcome of patients with complex CHD at 24 months of age and identify a subgroup with poorer outcome
2. To evaluate the utility of fetal and postnatal (preoperative and postoperative) diagnostic techniques for early recognition of patients at risk for altered neurologic outcome
3. To develop and validate predictive algorithms of poor later neurodevelopment in CHD patients

DESCRIPTION OF WORK

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

Max. 6,500 characters

Six Spanish referral centres for CHD included will participate in this WP. A prospective multicentre case-control study will be carried out. Foetuses with CHD (transposition of great arteries, tetralogy of Fallot, hypoplastic left heart syndrome and septal defects) will be studied from 24 weeks of gestation to 2 years of age. The recruitment target for this study is 300 patients. Dr Cabañas is an expert in the field of neonatal and neurological disease. He will coordinate the following task among the participating groups:

4.1Harmonization of interdisciplinary research activity (Cabañas)
4.2 Preparation documents for Ethical Committees approval (Cabañas)
4.3 Patient enrollment into the study: Diagnostic tests will be repeated throughout the study in all patients, from the foetal period to 24 months of age, and will include: foetal cerebral haemodynamic Doppler assessment, functional echocardiography, brain MRI, regional cerebral oxymetry, electroencephalography and serum neurological and cardiac biomarkers (All).
4.4 Children neurodevelopment assessment: Neurodevelopmental assessment will be made at 12 months of age using the ages and stages questionnaire (ASQ) and at 24 months of age with the Bayley-III test (All)
4.5 Laboratory analysis of samples and biobank (All)
4.6 Statistical analysis (All)
4.7 Integration of data on predictive algorithms of poor later neurodevelopment in CHD (Cabañas, Llurba)
4.8 Guidelines and protocols for prevention of adverse neurodevelopment in CHD (All)
4.9 Preparation for biomarkers patens and future industry interests and spin off (All)
4.10 Preparation for any future interventional studies (All)

DELIVERABLES

Brief description and date of delivery

Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained

1) Neurodevelopment assessment at 12 and 24 months of age in children with different types of CHD

2) Obtain prospective measurements on distinct fetal, neonatal and surgery variables and its correlation with the neurodevelopment risk factors in an integrated database
3) To develop and validate predictive algorithms of poor later neurodevelopment in CHD patients able to be used as clinical tools by cardiologists and obstetricians and for parental assessment

MILESTONES

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

This WP will provide the larger sample size than ever studied before in CHD over a period of five years that will permit: 1. sufficient recruitment for fetuses to be assigned depending on their CHD; 2. prospective follow-up and integration of data from the prenatal period to early childhood; and 3. Development of individualized solutions by creating true individual algorithms

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

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	PRE-NATAL ENVIRONMENT AND IT'S INFLUENCE ON PLACENTAL DYSFUNCTION AND FETAL HEART DEVELOPMENT AND CARDIOVASCULAR DISEASE LATER IN LIFE				

PI Family Name	GÓMEZ	VENTO	LLURBA	GARCÍA	LARQUÉ	MESA		
Group Nº	5	2	1	6	9	11		
Nº of Resarchers	11	17	12	10	5	5		

OBJECTIVES

Max. 1,200 characters

1. To assess the association between maternal and fetal biomarkers of placental dysfunction and exposure to air pollution compounds and heavy metals (cadmium, mercury and lead) during pregnancy
2. To assess the association between heart function and structural outcomes and exposure to air pollution compounds and heavy metals during pregnancy
3. To assess the association between placental vascular, inflammation and oxidative stress biomarkers and exposure to air pollution compounds and heavy metals during pregnancy.
4. To create and validate an animal model to study the extent of the impact of air pollution compounds and heavy metals in cardiovascular targets in maternal and offspring.

DESCRIPTION OF WORK

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

Max. 6,500 characters

This WP will include a population-based cohort of 600 women at 28 weeks of gestation subdivided according to estimated air pollutant concentration obtained from Public Health Barcelona geographical maps of pollution. Since the study has an obstetric and a neonatal component, both professional obstetricians and neonatologist groups will work closely to achieve relevant results at a maternal and a neonatal level. The leader of the workpackage will supervise obstetric and neonatal tasks in the intellectual and clinical work that will be reflected in protocols, abstracts, peer reviewed papers. In order to achieve the aims of this WP, the network will perform the following tasks under the leadership of Dr M Dolores Gómez-Roig:
5.1 Harmonization of interdisciplinary research activity (Gómez)
5.2 Preparation documents for Ethical Committees approval (Gómez)
5.3 Retrospective analysis of pollution areas and placental dysfunction parameters: To study the association of ozone (O3), carbon monoxide (CO), sulfur dioxide (SO2), nitrogen oxides (NOx), liquids, and particulate matter (PM) in air pollution and heavy metals in the pregnant healthy population with fetal biometrics and fetoplacental Doppler (All).
5.4 Retrospective analysis of pollution areas and fetal cardiovascular function To study the association of ozone (O3), carbon monoxide (CO), sulfur dioxide (SO2), nitrogen oxides (NOx), liquids, and particulate matter (PM) in air pollution and heavy metals with fetal cardiovascular remodeling and function (All).
5.5 Laboratory analysis of samples and biobank To study the expression of vascular, inflammation and oxidative stress in placenta in association with air pollution compounds and heavy metals (Vento, Larque, Mesa)
5.6 Creation of animal model an animal model would be developed to extent the study of the implications of air pollution and heavy metals in maternal and fetal cardiovascular programming (García, Vento, Larque, Mesa)
5.7 Statistical analysis (All)
5.8 Guidelines and protocols for public agencies (All)
5.9 Preparation for any future interventional studies (All)

DELIVERABLES

Brief description and date of delivery

Max. 1,500 characters

1. The correlation between air pollutants levels and heavy metals in maternal blood, cord blood and placenta with maternal and fetal biomarkers of placental insufficiency will be determined
2. Fetal cardiovascular remodeling and function in relation to different air pollution compounds and heavy metals exposure will be studied.

3. The expression of vascular, inflammation and oxidative stress in maternal blood and cord blood of women with different degrees of air pollution compounds and heavy metals exposure will be evaluated.

4. Experimental design and evaluation in animal model would shed light into the mechanism linking air pollution and heavy metals exposure and maternal and fetal cardiovascular programming

MILESTONES

Brief description and date of achievement

Max. 1,500 characters

Effects of air pollution and/or heavy metals on maternal and fetal health and heart programming will be analyzed to establish recommendations for public health practitioners to regulate air pollution compounds and heavy metals levels.

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	PRENATAL EXPOSURE TO ALCOHOL AND OTHER SUBSTANCES OF ABUSE AS AN ETIOLOGIC FACTOR OF POSTNATAL CARDIOVASCULAR DELETERIOUS EFFECTS							
PI Family Name	GARCIA-ALGAR	VENTO	PALLÁS	GÓMEZ	LLURBA	CABAÑAS		
Group Nº	6	2	4	5	1	3		
Nº of Resarchers	10	17	18	11	12	17		

OBJECTIVES

Max. 1,200 characters

6.1. To assess the vascular placental deleterious effects of prenatal exposure to alcohol and other substances of abuse
6.2. To assess the association between placentalbiomarkers(vascular, inflammation and oxidative stress)and prenatal exposure to alcohol and other substances of abuse
6.3. To follow up children prenatally exposed to alcohol about cardiovascular risk
6.4. To create and validate animals models in order to study prenatal exposure to alcohol and other substances of abuse as an etiologic factor of cardiovascular deleterious effects

DESCRIPTION OF WORK

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

Max. 6,500 characters

The leader of the workpackage will supervise tasks in the intellectual and clinical work that will be reflected in protocols, abstracts, peer reviewed papers. In order to achieve the aims of this WP, the network will perform the following tasks under the leadership of Dr Oscar García Algar, an expert in the field of toxical elements and maternal-child health:
6.1Harmonization of interdisciplinary research activity. Preparation documents for Ethical Committees approval (García)
6.2 Recruitment of pregnant women, newborns and children with prenatal exposure to alcohol and other substances of abuse Biomarkers of prenatal exposure to alcohol and other substances of abuse: maternal hair and meconium (All)
6.3 Placental study of angiogenic vascular effects of prenatal exposure to alcohol and other substances of abuse: macroscopic, microscopic, biomarkers (of exposure, damage, inflammation, epigenetics and oxidative stress) (All)
6.4 Statistical analysis (All)
6.4.1 Maternal-newborns dyads study: (1) association of prenatal exposure to alcohol and other substances of abuse with fetal cardiovascular remodeling and function; (2) expression of vascular, inflammation and oxidative stress in placenta in association with alcohol and other substances of abuse; (3) follow up of the dyads (All)
6.4.2 Follow up of children prenatally exposed to alcohol (adopted children from East Europe countries with Foetal Alcohol Syndrome (FAS)) (García)
6.5 Animal models (rat and zebra fish) to study the implications of alcohol and other substances of abuse in maternal and foetal cardiovascular programming (García, Vento)
6.6 Guidelines and protocols for public agencies (All)
6.7 Preparation for any future interventional studies (All)

DELIVERABLES

Brief description and date of delivery

Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1. List and description of vascular placental deleterious effects of prenatal exposure to alcohol and other substances of abuse
2. List and description of placentalbiomarkers (vascular, inflammation and oxidative stress)of prenatal exposure to alcohol and other substances of abuse
3. Prevalence, clinical cardiovascular and results derived from the follow up of the prenatally exposed cohort and mothers and children
4. Clinical cardiovascular and results derived from the follow up of the adopted children from East Europe countries (maternal-pregnancy and perinatal-neonatal outcomes)
5. Description of validate animal models of prenatal exposure to alcohol and other substances of abuse as an etiologic factor of cardiovascular deleterious effects

MILESTONES

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

Presentation of clinical practical guidelines about prevention, diagnosis, follow up and management of prenatal exposure to alcohol and other substances of abuse as an etiologic factor of postnatal cardiovascular deleterious effects.

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

LIST OF DELIVERABLES

DELIV. Nº	DELIVERABLE NAME	WP Nº	LEAD PARTICIPANT FAMILY NAME	DISSEMINANTION LEVEL	DELIVERY DATE
1	To identify the relevance of placental metabolic pathways related to apoptosis, inflammation, oxidative stress and angiogenesis according to the type of PE	1	VENTO	Public	30/6/2021
2	The identification of pathological pathways contributing to anti-angiogenic status in PE to generate potential therapeutic targets	1	VENTO	Public	30/6/2021
3	The relation between abnormal placental and brain angiogenesis in CHD fetuses would demonstrate the influence of prenatal mechanisms leading to poorer neurodevelopment in these children and open a window for prediction and prevention strategies	1	LLURBA	Public	31/12/2019
4	To reduce maternal and neonatal mortality-morbidity rate a 15%	2	LLURBA	Public	31/12/2021
5	Cost-effectiveness analysis of introduction sFlt1/PlGF ratio in the clinical practice	2	LLURBA	Public	30/6/2021
6	Feasible and effective interventions package to improve maternal and newborn health in women with PE	2	LLURBA	Public	31/12/2021
7	To establish correlation between the severity of cardiovascular dysfunction and angiogenic and anti-angiogenic factors in women and fetuses affected by PE/IUGR.	3	RODRÍGUEZ	Public	31/12/2020
8	To obtain a prenatal predictive algorithm for long-term cardiovascular maternal and foetal programme.	3	GÓMEZ	Public	31/12/2021
9	Creation and validation of an animal model of PE using injection of adenoviruses (Ad sFlt-1) to study the extent of the impact of placental insufficiency in cardiovascular targets.	3	LLURBA	Public	30/9/2018
10	Neurodevelopment assessment at 12 and 24 months of age in children with different types of CHD	4	CABAÑAS	Public	31/12/2021
11	Obtain prospective measurements on distinct fetal, neonatal and surgery variables and its correlation with the neurodevelopment risk factors in an integrated database	4	CABAÑAS	Public	31/12/2021
12	To develop and validate predictive algorithms of poor later neurodevelopment in CHD patients able to be used as clinical tools by cardiologists and obstetricians and for parental assessment	4	GÓMEZ	Public	31/12/2021
13	The correlation between air pollutants levels and heavy metals in maternal blood, cord blood and placenta with maternal and fetal biomarkers of placental insufficiency will be determined	5	GÓMEZ	Public	30/06/2020

14	The expression of vascular, inflammation and oxidative stress in maternal blood and cord blood of women with different degrees of air pollution compounds and heavy metals exposure will be evaluated	5	GÓMEZ	Public	31/12/2019
15	Experimental design and evaluation in animal model would shed light into the mechanism linking air pollution and heavy metals exposure and maternal and fetal cardiovascular programming	5	GARCÍA	Public	30/6/2021
16	List and description of vascular placental deleterious effects of prenatal exposure to alcohol and other substances of abuse	6	GARCÍA	Public	30/6/2021
17	Clinical cardiovascular and results derived from the follow up of the adopted children from East Europe countries (maternal-pregnancy and perinatal-neonatal outcomes)	6	GARCÍA	Public	30/6/2021
18	Description of validate animal models of prenatal exposure to alcohol and other substances of abuse as an etiologic factor of cardiovascular deleterious effects	6	VENTO	Public	31/12/2021

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

LIST OF MILESTONES

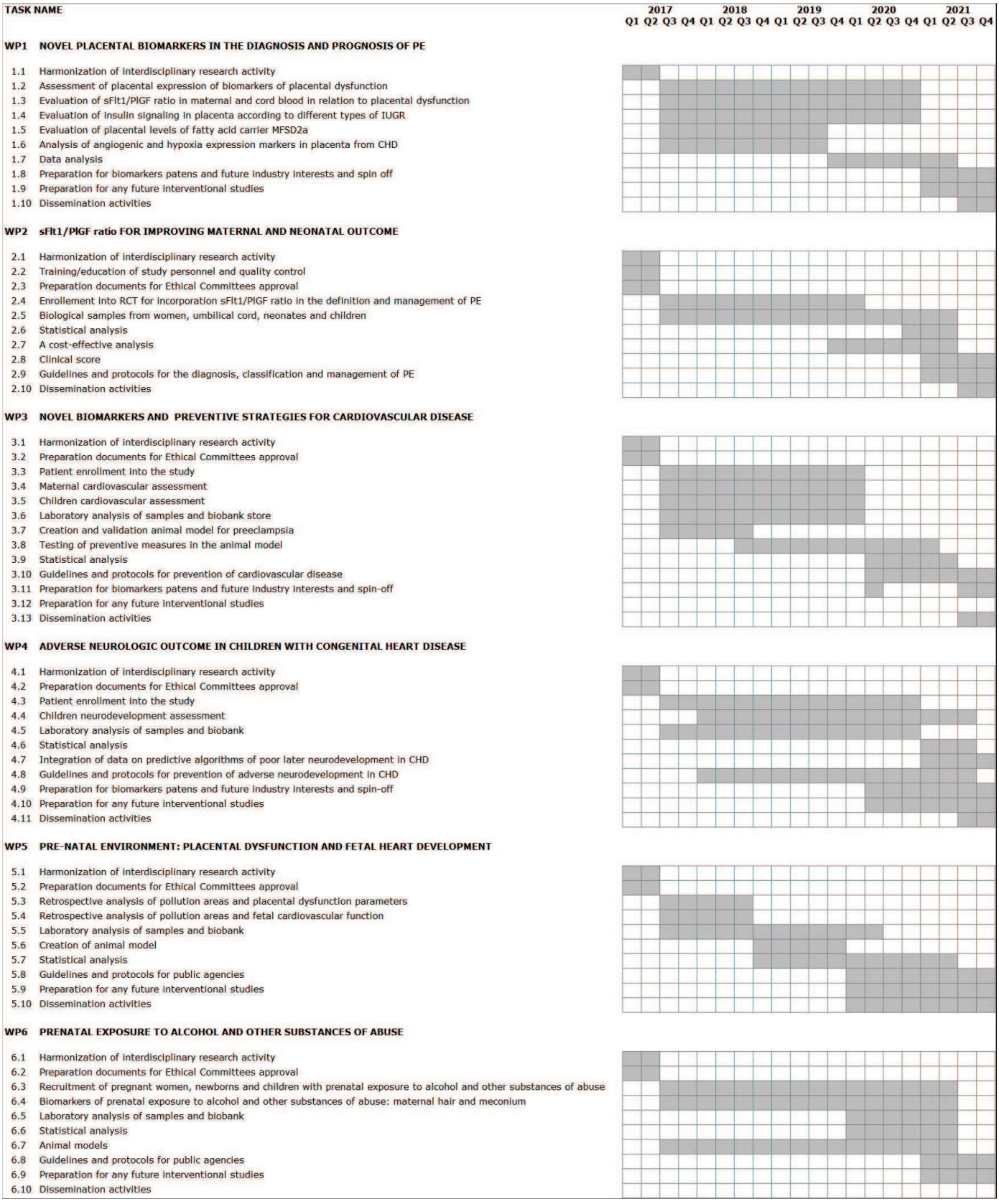
MILESTONE Nº	MILESTONE NAME	WP Nº	DUE DATE	MEANS OF VERIFICATION
1	An overview of the pathogenic mechanism leading to placental insufficiency according to its manifestations would be obtained to generate future hypothesis for target prevention and therapeutic interventions	1	31/12/2021	Scientific and technical reports patents of new biomarkers Peer reviewed scientific papers
2	To ascertain the utility of the incorporating of sFlt1/ PlGF ratio in the diagnosis and management of PE in order to change polices and improve maternal and neonatal health.	2	31/12/2021	National and International Guidelines for diagnosis and management of PE Database Patents new predictive tools Peer reviewed scientific papers
3	To provide the information of the relevance of prenatal biomarkers to identify mother and children at risk for cardiovascular disease later in life. The creation and use of an animal model of PE will give the opportunity to develop target strategies to improve cardiovascular health.	3	31/12/2021	Animal model PE and cardiovascular risk Guidelines for cardiovascular risk after placental complications Placenta and blood database and Biobank Patents new predictive tools Peer reviewed scientific papers
4	To provide the larger sample size than ever studied before in CHD over a period of five years that will permit: 1. sufficient recruitment for fetuses to be assigned depending on their CHD; 2. prospective follow-up and integration of data from the prenatal period to early childhood; and 3. Development of individualized solutions by creating true individual algorithms	4	31/12/2021	Clinical score for adverse neurodevelopment in CHD childen Protocols for improve neurodelopment in CHD Database and Biobank Patents new predictive tools Peer reviewed scientific papers
5	Effects of air pollution and/or heavy metals on maternal and fetal health and heart programming will be analyzed to establish recommendations for public health practitioners to regulate air pollution compounds and heavy metals levels.	5	31/12/2021	Recommendations for public health practitioners to regulate air pollution Database and Biobank Peer reviewed scientific papers
6	Presentation of clinical practical guidelines about prevention, diagnosis, follow up and management of prenatal exposure to alcohol and other substances of abuse as an etiologic factor of postnatal cardiovascular deleterious effects.	6	31/12/2021	Toxicological Guidelines for the Perinatal period by the Health Ministry Database and Biobank Animal model Peer reviewed scientific papers
7				
8				

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

SCHEDULE / TIMELINE

Please provide a diagram

Max. 1 figure (jpg format)



RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

MANAGEMENT/COORDINATION OF WORK PACKAGES

Please provide a written description. Max. 1 page

The overall medical-scientific coordination of the programme 2 will be in the hands of Dr. Elisa Llurba at HUVH (PI group 5), that would act as a Programme 2 coordinator with the collaboration of the coordinator of the Network, Dr Max Vento. The coordination between SAMID work packages that involve randomized control trials, clinical research and experimental studies will be run by the **programme #2 coordinator**.

The Coordinator of the Programme #2 who responsible for the Placental Insufficiency Unit in Vall d'Hebron University Hospital has in-depth knowledge of advanced and current standards for delivering medical care in pregnancy and has a vast experience in design and accomplishment of clinical trials, methodology (molecular biology and genetic and mass spectrometry platforms), leadership and experience in advance research studies and writing of clinical protocols.

The Assistant Manager to the coordinator who is at present the Manager of the Network (A Tenería) to run the financial and administrative tasks of the project and prepare the Reporting towards the Carlos III Institution.

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.
The **daily Management Team** is formed by the Programme Coordinator, the Assistant Manager and the Scientific Assistant to the Programme Coordinator, and will work in close connection with the Group Leaders

The **Project Management Board (PMB)** is the overall joint decision-making body holding final responsibility for the quality of the results, the major decisions regarding reporting, disputes and financial control, etc. It is formed by one member from each group with equal rights of vote representation during the joint decision meetings.

The PMB will provide general coordination in scientific issues and holds final responsibility for the Programme. Its main duty will be to organise the proper actions to administer the scientific life cycle of the project. This includes the following specific tasks:

a) to develop and implement the management tasks;
b) to define, develop and assign the scientific tasks;
c) to advise and direct the partners on the developments necessary for the project;
d) to monitor and supervise the progress of the scientific work;
e) to ensure that the partners perform and report their work in accordance with the agreed procedures and quality standards;
f) to coordinate the preparation of periodic activity reports and communications for scientific issues;
g) to schedule and approve dissemination activities; scientific workshops, meetings and training activities.

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

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:

Participating hospitals are among the largest centers for Maternal and Children health in Spain. To carry out this ambitious programme is essential the participation of several centers of excellence as the only strategy to meet the objectives, given the need for a large enough sample,expertise and multidisciplinary network within a reasonable time.

The coordinated project offers a clear added value far greater than the simple sum of individual projects:

1. Sample size: coordinated project will ensure sufficiently large sample sizes for specific pathophysiological groups described in the previous section and almost never reported in the literature.
2. Ability to perform the first large prospective study from prenatal to early childhood. There is no study of this type with data integration of pre- and post-natal, or attempts to integrate prenatal and perinatal complex information.
3. Providing pre-clinical solutions with capacity for immediate validation through the establishment of the collaborative network, which guarantee these future studies in the same field of the consortium that is created in preparation for the project.
4. Development of solutions focused on personalized medicine. Ambition and sample sizes achieved statistical allow a degree of power that will make it possible to have true individualized risk algorithms.
5. Establishment of synergies between overhead lines stable high performance multidisciplinary, incorporating basic research groups (biologists and bioinformatics) and clinical (Fetal Medicine, neonatologists, cardiologists, intensivists, neuroradiologists and neuropsychologists, pediatricians, surgeros, anestesiologist)
6. Creating a database and a single theme biobank in Europe. Database and biobank will be available to new studies in the samid RED and SNS and other initiatives.
7. Translational research and capacity building and competitiveness of the SNS. Complications of pregnancy (PE and IUGR) affect 15% of pregnancies but the incidence of complications is rare or under-reported. On the other hand, congenital heart diseases (CHD) alveit, are the most common congenital abnormality, each of them is rare. Therefore the summ of individual groups will provide a outestanding database that would reach enough samples to obtain meanful and clinical answers to the clinical problems aimed to be resolved in the programme

8 Creating talent within the network.

9. Dissemination of good practices through protocols agreed clinical management and mobility and transfer of technical, clinical and scientific knowledge among members.
10. Opportunity for new initiatives internationally. The availability of a database and a biobank important about this pathology favor to enter the international initiatives and expected results to qualify for new sources of international finance.
11. High social impact. SNS translation result in a great impact on the quality of life of these mothers and children. The wide coverage provided by the centers can count on the support of families of children and people with complication of pregnancy.

Scientific relationship between the different research groups in the proposed research topics:

The programme will coordinate existing large projects in this field in Spain and get high value-added synergies by combining complementary methodologies and approaches. A lattice structure schemes will

be available following previous projects carried out by the network and research groups.The strengths of SAMID action are our strong epidemiological, clinical and laboratory science networks that are focussed on pregnant women, paediatrics and congenital diseases and our expertise and established track records in these research areas. Within the network there is over 20 years of experience of conducting national and international research on preeclampsia, cardiovascular dysfunction in growth restriction, nutrition, neurodevelopment, prematurity and obesity, with a particular focus on cohort studies linked to strong laboratory science. We therefore have the required "know-how" and experience to answer the pressing questions regarding maternal, perinatal and pediatric health.

There is a powerful and established synergy within SAMID network that have provide the resources to develop seven different lines of research: 1) neonatal adverse nutritional and metabolic outcomes and possible preventive nutritional strategies.; 2) Angiogenic factors and uterine artery Doppler in the prediction of PE and IUGR; 3) Maternal, fetal and children cardiac function in IUGR: cardiovascular program; 4) Preterm birth: prevention of brain damage; 5) environmental factors associated with neurologic, nutritional, and metabolic conditions in the perinatal and childhood periods.; 6) indicators and biomarkers to early predicting neurocognitive and developmental outcomes and identify risk factors for neurologic sequelae; 7) Experimental and clinical Fetal Therapy. In the last 8 years this group has obtained several national grants and is actually coordinating five clinical trials and It is also involved in other international clinical trials. This group has generated more than 200 original papers published in high impact factor international medical journals.

Seven centers will carry out different WP task at the clinical level (1, 2, 3, 4, 5, 6, 8, 10) and therefore have common objectives and design. Two further involved with the determination of biochemical and placental markers of injury (1, 5, 7, 10, 11, 13).

Longitudinal WP studies, including the activities of cases and data collection are arranged in sequence forms three blocks:

· Block 1: Prenatal. Coordination by Obstetric investigators of the participating groups.

·Block 2; post-natal immediately. Coordination Pediatrics (includes neonatal, pediatric, and intensive cardiology).

· Block 3: long-term monitoring (pediatric cardiology and neuropsicologist)

7 transversely platforms for execution, each with unique or shared responsibility between centers, with the goals will require that:

· coordinate the definition of joint protocols:

· monitor compliance with quality objectives:

· ensure the dissemination of good practice;

· integration of data centrally.

They are described in outline platforms provided:

· Platform databases (coordinates_Group5): web platform samid RED (http://www.redsamid.net/) integrated software tools, protocols and electronic data bases developed under project (https: // w3.icf. uab.es/nexus).

· Platform image Doppler ultrasound and cardiac function (Group 2, 4, 5 and 1coordinate)

· Platform biobanks and biomarkers coordinated project (Group 1, 7, 11, 13 coordinate): definition of standards, databases and circulation of samples

· Neuropsychological monitoring platform (Group 2, 4, 5)

· Cardiovascular monitoring platform (2, 4, 5 and 10 coordinate)

· Platform data analysis (Group 1 and 5 coordinate)

Describe the management of the intellectual property

The Programme coordinator is responsible for the coordination of dissemination and protection activities, ensuring that the results are adequately disseminated and do not cause conflicts of interest among partners.

The legal framework of the consortium will be Represented by a Consortium Agreement (CA), to be signed During month 1. The CA will Essentially Contain the following points:

a) the internal organization of the consortium, governance structure, roles and Responsibilities, decision-making processes and management arrangements; b) arrangements for the distribution of the

partners contribution; c) Provisions for the settlement of internal disputes, treats including cases of abuse of power; d) any other Provisions Necessary to Ensure a sound management of the project.
To this end, he will establish appropriate links with external agencies and bodies engaged in implementation activities. The strategy will allow the scientific knowledge generated by the consortium to be actively disseminated amongst academic communities to validate it and amongst stake holders to ensure its take up. The full range of scientific, technological and product/process/system specific dissemination activities will be enabled without compromising the protection of the foreground IPR.

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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 2 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 2 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

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

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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. Potencial impact on health population

· Our approach to this programme is, at the highest level, to put Spanish based best practice expertise to help facilitate the implementation of optimum solutions at the service of Maternal and Children heath. The partnership itself has been strategically designed to achieve our objectives. It is a constellation of clinical, laboratory and experimental investigators

· The solution we are offering has also been carefully and strategically designed. Too often one aspect of the solution to maternal and neonatal health has been prioritised over other key aspects. In response to this tendency we have put together a fully integrated network of investigators which addresses as many aspects of the problem as we could feasibly deal with in one intervention. So, in summary, our, we would characterise our strategic approach in this programme as systemic and integrated both in terms of the team, the specific solutions offered and also in terms of longer term benefits on maternal and children health.

· Although the PE, IUGR and CHD are not common, as a whole the project focuses on a prevalent disease such as risk of cardiovascular disease of prenatal origin affecting 3 in 10 adults and found in one of the priority lines of research AES and in perinatal medicine

· The results allow advancing in the early detection of disease processes.

· The programme will develop biotechnological applications for clinical use in order to improve diagnosis and cover the current lack of tools for early identification.

· The application of clinical solutions is aimed at reducing the burden of disease on society, by enabling early interventions in the early period of cardio-developmental and consequently reduce emotional, social and economic burden they produce.

· The programme aims to generate solutions of personalized medicine in order to treat individually to patients performing interventions on individuals and not populations at risk, thereby maximizing system efficiency by substantially reducing the economic cost as it will stop intervene in subjects not required and improving the effect on the population if required to intervene early.

· The results will promote research into new preventive interventions aimed at preventing cardiovascular programming during fetal life or reduce their impact on neurodevelopment.

2. Potencial impact on National Health System

· The programme has a high capacity for translation to SNS. This is a programme that allows for the first time the NHS provided a clinical and research synergy in which the largest centers of a country involved

in the same thematic.

· The databases and biobanks generated within the SNS are single size in Europe, which will be available to other groups of SNS for exploitation in complementary projects on rare diseases or cardiovascular developmental in general.

· This synergy will be consolidated in future strategies, as the capacity and size of the consortium created will allow the development of solutions at an early stage in order to shorten the translational phase towards real clinical solutions. This will create pioneering clinical solutions at the international level to be applied at an earlier stage in our system.

· As described in the group experience, size, competitiveness and ability of international relations of the senior researchers associated within this project will certainly contribute to create synergies and participation in international initiatives, and to join major initiatives from the European networks framework program.

· There linkage and experience with intellectual protection and promotion of spin-off. The project is of great potential interest to the industry for its high potential to result in marketable applications

· The project promotes talent and human capacity of the NHS:

- By following the career of young postdoctorals and predoctotal researchers with leadership skills for a pioneering initiative;

- By training and consolidation of supradisciplinary researchers in highly competitive and focused on developing clinical solutions, high transfer component results in clinical practice fields.

- Creation of new technologies based on personalized medicine and integration of new technologies with clinical data on advanced algorithms

- Potential pharmaceutical and technologic patents would be derived from the programme

3. Clinical guidelines or other contributions to national and international standards; patents

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, M. Vento) has a special interest in involving parents and greater public in the research process, as well as the research community and other stakeholders)

Patients will be kept abreast of all scientific developments within the SAMID action work programme relevant to the prevention, detection and treatment of cardiovascular and neurological risk factors through engagement with patient organizations and activist groups and the production of specific communication materials. The SAMID network will work to engage and interact with patient organizations representing mothers, infants, and children and focusing on perinatal disease and disability, seeking out and actively collaborating with local entities.

SAMID network programme will engage healthcare providers directly at partner sites through the development and dissemination of educational materials and other training activities conveying key messages on Project results regarding the detection and treatment of complications of pregnancy and long term consequences in mothers and children. The wider clinical community will be reached through scaling up of these educational activities, preparation of peer reviewed publications in open access

journals, presentation of project results at international conferences in the field, and collaboration in updating or creating specific diagnostic and clinical treatment guidelines

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 of Perinatal Medicine, International Society of Ultrasound in Obstetrics and Gynecol (ISUOG), International Federation of Obstet Gynecol (FIGO), 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:
- Clinical guidelines
- 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.

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EXPECTED IMPACTS SET OUT IN THE WORK PROGRAMME

Please bind each objective with its expected impact.

Programme: CARDIOVASCULAR RISK-RELATED PRENATAL FACTORS

OBJECTIVES INCLUDED	EXPECTED IMPACTS
1) SAMID network will get insight into the preclinical research on the molecular mechanisms that determine abnormal placentation and dysfunction in order to provide novel placental biomarkers in the diagnosis and prognosis of preeclampsia.	To obtain novel placental biomarkers in the diagnosis and prognosis of preeclampsia. Development of cot-side diagnostic and prognostic biomarkers leading to patents, spin off and industry interest Creation of new technologies based on personalized medicine and integration of new technologies with clinical data on advanced algorithms Scientific and peer review papers
2) SAMID will provide evidence that the re-definition of preeclampsia as an entity caused by a placental unbalance of angiogenic and anti-angiogenic factors and its incorporation in the diagnosis and classification of the disease would improve maternal and neonatal health.	Guidelines for definition and classification of PE for early identification of women at risk for adverse outcome Improvement of the diagnosis and outcome for PE in the clinical setting To decrease maternal morbidity and mortality To reduce hospital stay and cost from unnecessary interventions in women with the suspition of PE Score with a prediction algorith for adverse outcome in PE, leading to mobile application and patents and spin off or industry interest Databases and biobanks generated with a single size in Europe, which will be available to other groups of SNS for exploitation in complementary projects on PE. Scientific and peer review papers
3) SAMID group will study novel maternal and children cardiovascular risk biomarkers and to explore potential preventive strategies to help those cases at increased risk for cardiovascular and metabolic programming.	Promoting basic and clinical research in the fields of prenatal and postnatal risk factors for cardiovascular risk Integrate novel strategies to improve maternal and children cardiovascular health Development of cot-side diagnostic and prognostic biomarkers leading to patents, spin off and industry interest To generate solutions of personalized medicine Scientific and peer review papers
4) Prenatal and postnatal factors involved in the etiology of adverse neurologic outcome in children with congenital heart disease will be assessed and the development of individualized solutions by creating true individual algorithms will be provided by SAMID team.	Obtain prediction tools (imaging, biochemical biomarkers) for adverse neurological conditions affecting children with congenital heart disease. Databases and biobanks generated with a single size in Europe, which will be available to other groups of SNS for exploitation in complementary projects on CHD Enabling early interventions in the early period of cardio-neurodevelopmental and consequently reduce emotional, social and economic burden in the society To generate solutions of personalized medicine in order to treat individually to patients performing interventions on individuals Scientific and peer review papers
5) SAMID network will study pre-natal environment and its influence on placental dysfunction and fetal heart development and cardiovascular disease later in life.	Provide recommendations for public health practitioners to regulate air pollution compounds and heavy metals levels to avoid its detrimental effects in pregnancy Epidemiology of exposure to air pollutans and heavy metals by pregnant women and offspring Guidelines informing on the risk of exposure Scientific and peer review papers

OBJECTIVES INCLUDED	EXPECTED IMPACTS
6) SAMID will provide light into the identification of mechanism (pathological, biochemical and epigenetic changes) through which drugs induce their deleterious effects in fetal development	To know te effects of prenatal exposure to alcohol and other substances of abuse contributes to prenatal cardiovascular programme Epidemiology of exposure to legal and illegal toxics by pregnant women and offspring Guidelines informing on the risk of exposure Animal models to study cardiovascular consequences of toxic substances Scientific and peer review papers

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SUMMARY OF THE IMPACTS INDICATORS

Please for each expected impact bind its measurement indicator.

Programme: CARDIOVASCULAR RISK-RELATED PRENATAL FACTORS

IMPACT	INDICATOR	TYPE	EXPECTED TIME OF ACHIEVEMENT	EXPECTED OUTCOME
Guidelines for PE diagnosis and management	Scientific reports after selective observational and intervention trials	Qualitative	31/12/2021	National and International recommendation
Clinical algorith for prediction of adverse outcome in PE	Scientific reports after selective observational and intervention trials	Qualitative	31/12/2021	Mobile app
Novel placental Biomarkers predictive of cardiovascular disease related to conditions studied in programme 2	Scientific reports after selective observational and intervention trials	Quantitative	31/12/2020	Patents
Protocols for early detection and treatment of cardiovascular risk after placental complications	Publication in the Spanish Society of Obstetrics and Gynecology	Qualitative	31/12/2021	National and International recommendation
Protocols of early detection and treatment of conditions putting infants and children at risk of cardiovascular disease later in life	Publication in diferent Pediatric and Obstetric Societies Recommendation to Spanish Health authorities	Qualitative	31/12/2021	Recommendation to Spanish Health authorities
Protocols of early detection and treatment of conditions putting infants and children with at risk of impaired neurodevelopment	Publication in diferent Pediatric and Obstetric Societies Recommendation to Spanish Health authorities	Qualitative	31/12/2021	Recommendation to Spanish Health authorities
Reduction of maternal morbidity and mortality due to PE	Reduction of maternal morbidity and mortality indicators from diferent centers	Quantitative	31/12/2020	Peer reviewed papers Recommendation to Spanish Health authorities
Reduction hospitalization cost in women with suspiction of PE	Reduction of maternal days of hospitalization from diferent centers	Quantitative	30/6/2020	Peer reviewed papers Recommendation to Spanish Health authorities
Databases generated from various prenatal and postnatal conditions related to studies from programme 2	Databases	Quantitative	31/12/2021	Exploitation in complementary projects on perinatal conditions
Biobanks generated from various prenatal and postnatal conditions related to studies from programme 2	Biobanks	Quantitative	31/12/2021	Exploitation in complementary projects on perinatal conditions

Early interventions in the early period of cardio-neurodevelopment	Obstetric and Paediatric Socienty guidelines	Qualitative	31/12/2021	To reduce emotional, social and economic burden in the society
To generate solutions of personalized medicine in maternal and children conditions able to perform interventions on individuals	Obstetric and Paediatric Socienty guidelines	Qualitative	31/12/2021	To improve quality of SNS
Recommendations for public health practitioners to regulate air pollution compounds and heavy metals levels	Recommendation to Spanish Health authorities	Quantitative	31/12/2021	To avoid its detrimental effects in pregnancy and childhood
Guideline for avoidance of alcohol and drugs abuse consumption during pregnancy	Recommendation to Spanish Health authorities	Quantitative	31/12/2021	Recommendation to Spanish Health authorities
		Select		
		Select		
		Select		

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COMMUNICATION PLAN OVERVIEW

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

Programme: CARDIOVASCULAR RISK-RELATED PRENATAL FACTORS

STAKEHOLDERS OR TARGET GROUPS	ACTIVITY OR CHANNEL	PURPOSE	PARTNERS/GROUPS
Obstetric and Pediatric Societies at a National and International lebel	Presentation Results in congressess Peer reviewed publications Uploading files in Webpages Collaboration with working groups	Expand findings and improve guidelines and protocols	National and International Societies of Obstetrics and Gynecology Pediatric subespecialities Neonatologist, biochemestries, Industries
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 Programme 2
Spanish Government	Direct communication	Cooperation with public stakeholders to implement recommendations from Programme 2 studies	Local public health institutions, AEMPS; ISCIII, National Ministry od Health, Ministry of Education
Pharmaceutic industries	Direct contact trought innovation secctions of the research institutes	Enhance cooperation and creation of spin off	AEFI Farmaindustry

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REQUESTED BUDGET

DETAILED BUDGET FOR THE PROPOSED RESEARCH PROGRAMME

GROUP Nº	1	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 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		6,000	Scientific Peer reviewed publications Shipment of biological samples
TRAVEL		6,000	The Coordinator has to performed meetings every year with the various IPs of the Programme 2 (11) and present data at international congresses representing the Spanish Network.
TOTAL		€ 41,500	

GROUP Nº	2	PI SHORT NAME	VENTO
		COST (€)	JUSTIFICATION
PERSONNEL		29,500	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.
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	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	4	PI SHORT NAME	PALLÁS
GROUP Nº	4	PI SHORT NAME	

GROUP Nº	4	PI SHORT NAME	
		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	5	PI SHORT NAME	GÓMEZ
		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	6	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	7	PI SHORT NAME	LOPEZ-HERCE
		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	8	PI SHORT NAME	RODRÍGUEZ
GROUP Nº	8	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 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	9	PI SHORT NAME	LARQUÉ
		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	Meetings of the Network Presentation of results
TOTAL		€ 33,500	

GROUP Nº	10	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	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	

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RD16/0022/0015	ELISA LLURBA OLIVÉ

REQUESTED BUDGET

BUDGET JUSTIFICATION

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

The Programme 2 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 1.622.500,00 € (including one post-doctoral position, predoctorals positions and a technician during 5 years)
The groups involved in the Programme 2 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.

The full time researcher will:
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 2
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.

Full time Scientific Assistant to the Coordinator of Programme 2
The enormous complexity of coordinating 11 research groups with a total of approximately 120 researchers involved in complex experimental and clinical studies requires a substantial support. The post-doctoral contract will be used for a **scientific assistant,** that 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. 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 11 groups in the Programme 2 and of the Working Package groups in the Programme 1 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. Assistant coordinator and Programme lider will have the support of SCREN (**www.scren.es**) that is present in HUVH and in the other partners of programme 2.

2. Good and Services.
The clinical groups will have to keep samples in the Biobank and 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 and 2 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 and 2. Coordinator of Programme 2 will have to travel frequently to the different sites participating and will represent our Network in International Workshops, conferences and European Union Clinical Trial meetings.

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

ANNEXES (Text)

Max. 2 pages (10,700 characters)

In WP2 "ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS (sFlt1/PIGF ratio) FOR IMPROVING MATERNAL AND NEONATAL OUTCOME" must bé included another group:

IP Family Name: LÓPEZ DE HEREDIA
Group nº: 10
Nº of researchers: 10

RETIC Code	Programme Leader:
RD16/0022/0015	ELISA LLURBA OLIVÉ

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.