

**PE37: A multicenter randomized trial of screening with sFlt1/PIGF and selective labor induction to prevent preeclampsia at term.**

<p><b>Primary Site:</b></p> <p>BCNatal (Hospital Clínic and Hospital Sant Joan de Déu) and Hospital Sant Pau, Barcelona, Spain</p>
<p><b>Principal Investigators:</b></p> <p>Francesc Figueras, Elisa Llurba and Eduard Gratacós</p>
<p><b>Disease Studied and Intervention</b></p> <p>Preeclampsia in late pregnancy</p>
<p><b>Cohort:</b></p> <p>Non-selected nulliparous pregnant women routinely attended at 35-36 weeks' gestation and randomized to revealed versus concealed maternal angiogenic factors levels.</p>
<p><b>Inclusion and Exclusion Criteria:</b></p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> <li>1. Nulliparous women</li> <li>2. Singleton pregnancies</li> <li>3. &gt;18 years old</li> <li>4. 35.0-36.6 weeks of gestation</li> <li>5. Maternal written consent form</li> <li>6. Planned vaginal delivery</li> </ol> <p>Exclusion criteria:</p> <p>-Any maternal or fetal complications that require labor induction before 38 weeks according to local institutional protocols (including established preeclampsia).</p>
<p><b>Study Type</b></p> <p>Prospective, open-label randomized multicentre study with parallel groups conducted at BCNatal (Hospital Clínic and Hospital Sant Joan de Deu) (Barcelona), Hospital Sant Pau (Barcelona), Hospital la Paz (Madrid), Hospital del Mar (Barcelona), Hospital la Fe (Valencia), Hospital Son Llatzer (Mallorca), Hospital Can Ruti (Badalona), Hospital Clínico de Zaragoza, Hospital Arrixaca de Murcia and Complejo Hospitalario Universitario Insular Materno Infantil (Las Palmas de Gran Canaria) (Spain), Institute for the Care of Mother and Child, Prague, Prague, Czechia, Centre of Postgraduate Medical Education, Obstetrics and Gynecology and Perinatal Medicine, Warsaw, Poland;</p>

Gynecology and Obstetrics - CHU Liège; Belgium.
<p><b>Intervention</b></p> <ul style="list-style-type: none"> <li>Revealed arm: Blood sampling at 35+0-36+6w to determine sFlt-1/PlGF ratio. The result will be known by managing clinicians and, if &gt;90th centile, labour induction from 37+0 weeks will be offered.</li> <li>Concealed arm: The result of sFlt1/PlGF ratio will be unknown. Routine follow-up</li> </ul>
<p><b>Duration</b></p> <p>3 years</p>
<p><b>Date Of First Enrolment</b></p> <p>February 2021</p>
<p><b>Estimated Sample Size</b></p> <p>8302 nulliparous women are needed to demonstrate a 50% reduction of development of PE (from 1.5%) with a 90% power and a 5% alpha-risk. Assuming a 10% loss, we estimated a sample size of 9132 women.</p>
<p><b>Study Aims</b></p> <p>To evaluate the impact of a policy of induction of labour from 37 weeks of gestation in nulliparous women at risk for preeclampsia as defined by a sFlt1/PlGF ratio &gt;90th centile at 35-36 weeks of gestation on the prevalence of term PE.</p> <p>As secondary objectives, the study will evaluate the impact of the sFlt1/PlGF screening on:</p> <ol style="list-style-type: none"> <li>Cesarean section rates</li> <li>Perinatal morbidity</li> <li>Maternal pregnancy-related morbidity.</li> <li>Maternal post-pregnancy endothelial function.</li> <li>Cost-efficiency analysis (hospital maternal and neonatal stay and incurred costs).</li> <li>Maternal experience.</li> </ol>

### Executive summary

- Preeclampsia (PE) affects ~5% of pregnancies. Although improved obstetrical care has significantly diminished associated maternal mortality, PE remains a leading cause of maternal morbidity and mortality in the world.
- Term PE accounts for 70% of all PE and a large proportion of maternal-fetal morbidity related with this condition. Prediction and prevention of term PE remains unsolved.

- Previously proposed approaches are based on combined screening and/or prophylactic drugs, but these policies are unlikely to be implementable in many world settings.
- Recent evidence shows that sFlt1-PlGF ratio at 35-37w predicts term PE with 80% detection rate.
- Likewise, recent studies demonstrate that induction of labor (IOL) from 37w is safe.
- The investigators hypothesize that a single-step universal screening for term PE based on sFlt1/PlGF ratio at 35-37w followed by IOL from 37w would reduce the prevalence of term PE without increasing cesarean section rates or adverse neonatal outcomes.
- The investigators propose a randomized clinical trial to evaluate the impact of a screening of term PE with sFlt-1/PlGF ratio in asymptomatic nulliparous women at 35-37w. Women will be assigned to revealed (sFlt-1/PlGF known to clinicians) versus concealed (unknown) arms. A cutoff of >90th centile will be used to define high risk of PE and offer IOL from 37w.
- If successful, the results of this trial will provide evidence to support a simple universal screening strategy reducing the prevalence of term PE, which could be applicable in most healthcare settings and have enormous implications on perinatal outcomes and public health policies worldwide.

## **Background**

### **Preeclampsia at term as an unsolved problem with a high health impact**

Preeclampsia (PE), defined as the presence of hypertension with other signs of endothelial systemic damage, affecting 5-10% pregnancies and remains one of the most prevalent serious complications of pregnancy. Despite improved obstetrical care, PE remains a leading cause of maternal morbidity and mortality worldwide. While early-onset PE is the most feared form of the disease, a remarkable 70% of total cases occur at term (1), accounting for a large proportion of adverse maternal outcomes (2). Identification of term PE relies on clinical follow up and detection of hypertension in a pregnant woman, followed by elective delivery. This policies have been shown to reduce the rates of severe maternal complications and is now standard practice (3), but still result in a significant proportion of

cases detected too late (4). One important reason is that most instances of term PE occur in women without risk factors. Aside from the rates of severe complications, the diagnosis of PE entails a traumatic experience for women affecting their pregnancy and birth experience and their pathway to motherhood (5) (6). Moreover, PE has a significant impact in healthcare costs (7) and suffering PE predisposes women for long-term cardiovascular adverse outcomes later in life.

### Prediction and prevention of term preeclampsia

A strategy of prediction and prevention of PE in pre-clinical phases has long been sought, since it might avoid a high fraction of the severe maternal morbidity in pregnancy. Over recent years, this goal has been met for preterm PE, with a first trimester screening based on risk algorithms and prophylactic low dose aspirin (8). However, such strategies fail to predict and prevent term PE (9). Firstly, prediction of term PE by first or even second trimester shows very poor performance (R). Secondly, aspirin fails to prevent term PE (R).

However, term PE can be predicted with late pregnancy screening strategies. Recent evidence has shown that a late screening, at 35-36 weeks of gestation, is a successful approach in predicting PE. Thus, algorithms combining maternal risk factors, mean arterial blood pressure and angiogenic factors at 35-36 weeks' gestation predicted term PE within the next 2 and 4 weeks with detection rates (DR) of 92% and 72% respectively, for a 10% false positive rate (FPR). Interestingly, the performance of sFlt1/PlGF as standalone screening was remarkably high, with a DR of 82% and 62% for term PE within 2 and 4 weeks (Table 1) (10,11).

Table 1. Positive predictive value, and negative predictive value at the 10% screen-positive rate in screening for delivery with preeclampsia at <2 and <4 weeks from assessment by soluble fms-like tyrosine kinase-1/placental growth factor ratio (9)

Development of PE	Screen-positive rate	Detection rate	PPV (95% CI)	NPV (95% CI)	+LHR	-LHR

< 2s	10%	82%	3.8% (2.9-4.8)	99.90 (99.84-99.95)	8.2	0.2
<4s	10%	62%	8.8% (7.4-10.3)	99.38 (99.23-99.5)	6.2	0.42

However, whether there is an effective preventive strategy for reducing term PE remains to be proven. A recently finalized trial evaluated an approach based on late-pregnancy screening (using combined algorithms) followed by prophylactic statins. The trial is unpublished, but the authors have recently reported in congresses that prophylactic statins failed to show a reduction in the prevalence of term PE (Nicolaidis K, ISUOG 2020).

Preeclampsia, angiogenic factors, perinatal death, induction of labour

#### **Angiogenic factors: PlGF and sFlt1 and their role as specific biomarkers of PE**

For more than 100 years, PE was diagnosed by hypertension and proteinuria in a pregnant woman. Angiogenic factors have recently emerged as the most specific biomarkers of PE ever described, so much that are being incorporated as an essential component in the prediction, diagnosis and even prognosis of PE by all relevant international societies.

Under normal conditions, angiogenic factors released by the placenta maintain a balance in maternal blood whereby the effects of the proangiogenic Placental Growth Factor (PlGF) prevail over those of the antiangiogenic soluble fms-like tyrosine kinase 1 (sFlt1). In preeclampsia, placental inflammation and increased oxidative stress result in the release of larger amounts of sFlt1 over PlGF. Thus, the ratio sFlt1/PlGF reflects placental and endothelial functioning, the end-organs of preeclampsia, and it is a consubstantial feature of the disease.

This ratio has now been accepted as a criterion for the diagnosis of PE in suspected cases (12). According to recent studies in large populations, the capacity of an abnormal ratio in ruling-in the disease is intermediate-large (as reflected by a +LHR of 8.2), while its capacity in ruling it out is large (–LHR 0.2). This is in line with the high performance shown by the sFlt1/PlGF ratio to predict term PE at 35-36w. Thus, the sFlt1/PlGF ratio might represent a

feasible universal approach for the detection of risk by identifying term PE in its pre-clinical stages.

### **Justification of the study**

Finding an effective prediction and prevention for term PE remains an unsolved challenge. From previous recent evidence it seems clear that prediction very close to term may achieve a high detection rate, but there is no evidence as to which strategy might be effective in preventing PE in high-risk women. The investigators postulate that a solution that would be applicable in most settings worldwide would require a simplified, pragmatic, approach. The rationale of this proposal is that PE could be reduced with a single-step lab test screening followed by induction of labor (IOL).

**A single-step lab measure to detect PE.** Combined algorithms using angiogenic factors with Doppler ultrasound and maternal features seem to achieve the highest performance in detecting pre-clinical PE. However, the need to train staff and change pregnancy care protocols renders difficult generalization in high-resource and even more low-resource settings. On the contrary, single lab tests can be more easily incorporated into the mainstream clinical practice and provide a widespread solution for high-resource settings and specially sub-optimal healthcare systems heavily affected by the consequences of term PE. Angiogenic factors are the obvious candidate for these purposes. The sFlt1/PIGF ratio at 35-36w predicts term PE with a DR of 82% and is a standardized lab test nowadays, realizable by ELISA with widely available automated lab platforms. Normal values in late pregnancy have been reported and are fairly similar among different populations. As preliminary research for this study, the investigators have confirmed that the gestational-age adjusted normal values of sFlt1/PIGF matched quite remarkably those previously published in different populations across Europe. A one-step screening with sFlt1/PIGF would select a 5-10% of the population with the highest risk for PE.

### **IOL at 37 weeks as an intervention in women at high-risk for PE.**

Previous trials based on statins have failed to show a reduction of PE in high-risk women. IOL at 37 weeks is an alternative to avoid PE in those high-risk women. IOL has consistently been demonstrated to be safe (13) and does not affect long-term maternal quality of life (14). Both the HYPITAT and the DIGITAT randomized trials showed that IOL did not increase

caesarean rates or adverse neonatal outcomes (15). A recent large randomized trial in the US has shown that even in low-risk women, universal IOL decreased cesarean section rates and was well accepted (16). While in low-risk pregnancies labour induction has been found to be beneficial from 39 weeks (ARRIVE study), in women with placental-related conditions such as hypertension (HYPITAT) or small-for-gestational age (DIGITAT) it is 37+ weeks when the trade-off between neonatal and maternal benefits makes induction recommendable.

Therefore, the investigators hypothesize that a single-step universal screening for term PE based on sFlt1/PIGF ratio at 35-36.6 w followed by IOL at 37w in those women found to be at high risk might represent a feasible and reproducible strategy, applicable worldwide, to reduce the prevalence of term PE without increasing cesarean section rates or adverse neonatal outcomes.

### Objectives

To evaluate the impact of a policy of induction of labour from 37 weeks of gestation in nulliparous women at risk for preeclampsia as defined by a sFlt1/PIGF ratio >90th centile at 35-36 weeks of gestation on the prevalence of term PE.

As secondary objectives, the study will evaluate the impact of the sFlt1/PIGF screening on:

1. Cesarean section rates
2. Perinatal morbidity
3. Maternal pregnancy-related morbidity.
4. Maternal post-pregnancy endothelial function.
5. Cost-efficiency analysis (hospital maternal and neonatal stay and incurred costs).
6. Maternal experience.

### METHODOLOGY

#### Study design

Prospective, open-label randomized study with parallel groups.

#### Study population:

Non-selected nuliparous pregnant women routinely attended at 35-36 weeks' gestation and randomized to revealed versus concealed maternal angiogenic factors levels.

#### Inclusion and Exclusion Criteria:

Inclusion criteria:

- Nulliparous women

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- Singleton pregnancies
- >18 years old
- 35.0-36.6 weeks of gestation
- Maternal written consent form
- Planned vaginal delivery

Exclusion criteria:

- Any maternal or fetal complications that require labor induction before 38 weeks according to local institutional protocols (including established preeclampsia).

### 90<sup>th</sup> centile of sFlt1/PIGF ratio.

Calculation of sFlt1/PIGF ratio centile has been obtained from 600 serum samples from women with uneventful pregnancy outcomes attending BCNatal between 35.0 and 38.0 weeks of gestation (Figure 1). Samples were stored in BCNatal biobank and measured using automated electrochemiluminescence immunoassays on the Roche cobas platform (Roche Diagnostics GmbH, Mannheim, Germany) at the Biochemistry Dept. of Sant Pau Hospital. Intra- and interassay coefficients of variation were found to be <5%. Quantile regression analysis was applied for the establishment of the 90th centile value of sFlt1-1/PIGF at the midpoint of each gestational week. This value was considered as the cut-off for all the week interval: 25 between 35+0 and 35+6; and 35 between 36+0 and 36+6.

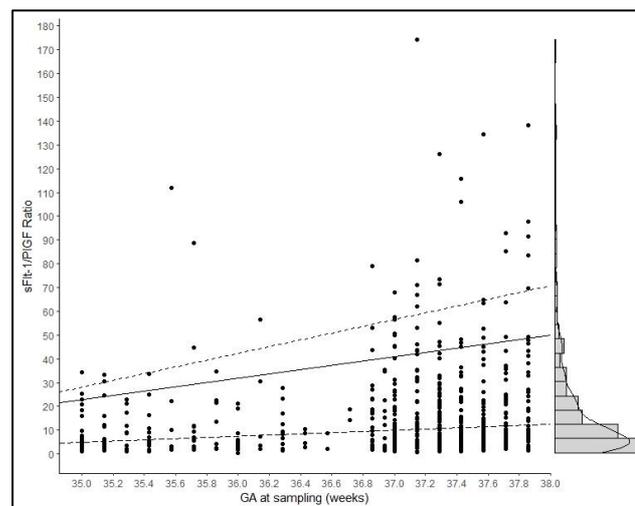


Figure 1. sFlt1/PIGF ratio from 35 to 38 weeks of gestation in normal pregnancies.

**Predictive variables**

Main predictive variable: study group, i.e. type of intervention.

**Outcome variables**

Main outcome variables: development of term preeclampsia.

Secondary outcome variables:

- Caesarean section rate
- Incidence of perinatal complications defined as the presence of placental abruption, severe fetal growth restriction (defined as birth weight <3rd centile), perinatal mortality, an Apgar score at 5-minute below 7.0, an umbilical artery pH below 7.10, need for respiratory support within 72 hours after birth neonatal intraventricular haemorrhage grade III/IV, necrotizing enterocolitis, periventricular leukomalacia, sepsis, bronchopulmonary dysplasia or hypoxic ischemic encephalopathy.
- Incidence of maternal complications, defined by a composite including any of the following: (i) HELLP syndrome (lactate dehydrogenase [LDH] >700 IU/L, AST to twice normal values and platelet count <100x10<sup>9</sup>/L); (ii) Central nervous system dysfunction (eclampsia, Glasgow Coma Score <13 (12), stroke, reversible ischemic neurological deficit or cortical blindness); (iii) hepatic dysfunction (INR >1.2 in the absence of disseminated intravascular coagulation, MELD score >10 (16), or hepatic hematoma or rupture); (iv) renal dysfunction (dialysis, serum creatinine concentration greater than 150 µmol/L, or urine output <0.5 mL/kg/h during 12 hours, according to renal insufficiency by RIFLE criteria; or need for treatment with furosemide to maintain urine output >0.5 mL/kg/h for 3 hours); (v) respiratory dysfunction (pulmonary edema, requirement of invasive or non-invasive mechanical ventilation, oxygen requirement greater than 50% concentration for longer than 1 hour, or severe breathing difficulty [no criteria of pulmonary edema but presence of dyspnea, crackles in pulmonary auscultation, and SaO<sub>2</sub><90%]); (vi) cardiovascular dysfunction (need for inotropic support, left ventricle failure, or myocardial infarction); (vii) placental abruption; or, (viii) a requirement for transfusion of blood products.
- Maternal blood pressure and endothelial function 6-months postpartum.
- Maternal and neonatal hospital stay duration (days).
- Maternal satisfaction and experience assessed by questionnaires (PSS, STAI, WHO and Labor Agency scale).

**Sample size calculation**

8302 nulliparous women are planned to be include demonstrating a 50% reduction of development of PE (from 1.5%). Assuming a 10% loss, the investigators estimated a sample size of 9132 women.

*R Syntax:*

```
library(SampleSize4ClinicalTrials)

ssc_propcomp (1L,ratio=1,alpha=0.05,power=0.9,p1=0.0075, p2=0.015)
```

Under a non-inferiority hypothesis testing design, assuming a composite adverse neonatal outcome incidence of 1% in the revealed group, 0.5% in the concealed risk and a prespecified non-inferiority margin of 0.25%; this sample size (4151 per arm) would result in a power of 99% to reject the null hypothesis that the reveal strategy increases the neonatal complications.

*R Syntax:*

```
library(SampleSize4ClinicalTrials)

ssc_propcomp (3L,ratio=1,alpha=0.05,power=0.99,p1=0.005, p2=0.01, delta=0.0025)
```

### **Randomization**

This will be an open-label randomized trial with parallel groups. An online service (<http://www.clinapsis.com>) will be used to generate a randomised sequence for the block of 1000 participants.

The allocation will be sequestered internally by a Clinical Trials Unit. After enrolment, recruiting physicians will obtain the allocation group from the Unit. Due to the nature of the interventionism it is not possible to blind participants or physicians from the Obstetric Department; however, obstetric management will follow similar protocols in each of the participating centers.

### **Data collection and analysis**

Study duration:

18 weeks maximum follow-up per patient, taking into account the period of intervention (5weeks) and puerperium (6 weeks) and follow-up visit at 6 months, assuming patients would delivery at less than 42 weeks of gestation. Recruitment will extent for 24 months (Figure 2).

Database: Data of participants included in the study will be codified and entered into an electronic case report form (<http://www.clinapsis.com>). All women included in the trial, independently on their randomization group, will provide a self-reported lifestyle questionnaires to measure anxiety and perceived stress (State-trait Anxiety Inventory-STAI(Spielberger 2010), Perceived Stress Scale-PSS(Cohen, Kamarck, and Mermelstein 1983), WHO Five Well Being Index(Bech et al. 2003)(Bonnín et al. 2018). Trained and certified research staff members will abstract information from medical records, including demographic information, medical history, and outcome data. Participants will be followed up with an interview performed by research personnel immediately and at 4-8 weeks post partum. During this inter- view, women will be asked to rate their experiences on the Labor Agency Scale (Hodnett 1987). A specific database will be designed for the study in order to protect patient confidentiality and register adequately all data for analysis; this database will be designed by the Bioinformatics Unit of the Epidemiology and Preventive Medicine Department of Sant Pau Hospital.

### **Statistical analysis**

Once all evaluations have been performed and laboratory determinations have been completed, the evaluation and analysis of the results will be carried out, with assistance of the Bioinformatics Department of the Institut de Recerca, and the Research Support Unit. Statistical analyses will be performed with the statistical package IBM® SPSS® Statistics Version 25 (IBM Corporation) or Open-source software (The R Foundation for Statistical Computing) will be used for all computations and graph construction (R V2.15.1). Statistical analysis will be based on the originally assigned groups (intention-to-treat). Normality of the distribution of variables will be evaluated with the Kolmogorov-Smirnov test. A binomial distribution model will be used to determine the 95% CI of proportions. Student's t-test (or non-parametric Mann-Whitney U test) and Pearson's  $\chi^2$  test or linear-by-linear  $\chi^2$  test (for trends across ordered categories) will be performed for univariate between-group comparisons of quantitative or qualitative variables, respectively. A mixed-effects logistic regression analysis of the incidence of live-birth with fixed effects for allocation group will be



## ETHICAL AND DISSEMINATION ISSUES

The project will be submitted for review and approval the Institutional Review Board for clinical research of each participating centre. The patients will be thoroughly informed prior to enrolment, and written informed consent will be obtained. This project is adhered to and assumes the principles of the Helsinki Declaration and the Europe Council of human rights and biomedicine.

### 1. USE OF PERSONAL DATA

Patients' information involved in the project will be managed under the rules for processing of personal data, as required by the European Directive 95/46/EC. According to this directive, the coordinator of the project is defined here as controller of data. Particularly, the following principles will be observed through appropriate measures:

- a) Legitimate acquisition and processing:
  - The information recorded will be relevant and not excessive, in accordance with the purposes of the objectives of the study, explicitly expressed in the information to patients.
  - The data will be processed only for the purposes defined in the study.
  - Unambiguous written consent will be obtained by the data subject in all cases.
- b) Information given to the data subject: the Informed Consent texts include clear information and purposes of the processing.
- c) The consent form will explain that if a participant wishes to withdraw from the study the data and samples acquired prior to that point will be retained. Reason for withdrawal will be recorded, if given, as will loss to follow up.

### 2. INFORMED CONSENT

Participants will be identified and screened according to the Inclusion criteria previously listed. If they are eligible and wish to participate, documented informed consent to take part in the trial will be obtained by a member of the research team. All members of the research team taking consent for screening and for the trial will have training in obtaining appropriate, valid, informed consent. If the participant wants more time to decide they will meet with a member of the research team at a subsequent visit.

Principal Investigators will have responsibility for writing the local Patient Information Sheet (PIS), which conforms to national requirements while also containing the essential information.

For women who cannot understand the official language of the participating hospital an interpreter would normally be present for the hospital appointment as part of their routine care. If no interpreter is present then a telephone interpreting service may be used or an interpreter may be arranged for the next hospital appointment. For women who can understand the spoken language but not the written PIS a member of the research team will read through the PIS with them and answer any questions. For women who have other communication difficulties (e.g. visual or hearing impairment) individual provisions will be made depending on the woman's preference. Any woman giving informed consent who cannot read the PIS herself will have her consent witnessed.

The woman's decisional capacity will be determined by the team member taking consent and no formal capacity instrument will be used. If there is doubt about capacity the woman will not be recruited. If a participant loses capacity during the trial no further trial-specific procedures will take place. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment or that of their child.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the Participant Information Sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

### 3. CONFIDENTIALITY AND SECURITY OF PROCESSING

-Personal Data will be encrypted through a process in order to guarantee anonymity. The identity of the data subjects will be kept only at a local level. Subjects will be identified by code numbers created at the first data transfer to the database.

-Data will be accessed only for statistical processing at a given intervals, by professional statisticians with no access to the personal information of the study subjects. Any person with access to data will be authorized by the controller of data, in this case the coordinator of the project. In the interim periods, no access to the databases will be permitted.

-The data collected in this project are not to be transferred or interchanged among others institutions.

-The coordinator shall implement the research project in full respect of the legal and ethical national requirements and code of practice.

#### 4. SAFETY PROVISIONS

The project will not pose any additional risk to the patients. The induction of labor will be performed only in foetuses at term, avoiding the potential risks related to prematurity. The diagnostic techniques are clinically accepted practice, (already used in other countries) and patients will receive information about this issue.

#### 5. PROTOCOL AMENDMENTS

Substantial protocol amendments may be proposed by any member of the Trial Team. They should then be reviewed by at least one representative from each trial centre. Responsibility for communicating substantial amendments will lie with the Trial Manager. They will inform Principal Investigators. Principal Investigators will have responsibility for informing their local and local regulatory bodies.

#### 6. DECLARATION OF INTERESTS

E. Llurba reports receiving fees for lectures from Thermofysher and serving on National Advisory Boards from Roche Diagnostics. F. Figueras reports personal lectures fees from Roche Diagnostics. The remaining investigators named on the protocol have no financial or other competing that impact on their responsibilities towards the scientific value or potential publishing activities associated with the interest trial.

#### 7. TRIAL RESULT

Trial results will be disseminated via:

-Scientific Societies/ Conferences/scientific meetings: an important part of the dissemination activities is the presentation of data at relevant meetings. The investigators will also run a major dissemination event at the end of the project at the World Association of Perinatal Medicine (WAMP) congress, a popular annual meeting which draws obstetricians, fetal medicine specialists, perinatologists and neonatologists.

-Scientific publications: through e-journals as well as high impact, international, peer reviewed publications; funds for open access are allocated to optimise dissemination.

The results of the trial will be disseminated regardless of the direction of effect.

Authorship policy: Any publication will be reviewed by all the PIs, each of which will lead the publication of at least one paper. All the PIs will be included as authors in all the

publications, and the decision on the first and last author of each publication will correspond to each participating centre leading it. The order of the other authors in between will be decided according to the number of patients recruited in each centre.

#### 8. ARCHIVING

The investigators agree to archive and/or arrange for secure storage of Clinical Trial materials and records for a minimum of 5 years after the close of the trial. Essential traceability documentation will be archived for a minimum of 30 years from the expiry date. in accordance with Regulation 1394/2007 and the applicable Directives therein. BCNatal will be responsible for archiving the Trial Master File for a minimum of 5 years and the Sponsor's traceability documentation for a minimum of 30 years.

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