Placental growth factor testing and planned early delivery for late preterm pre-eclampsia, compared to usual care in low- and middle-income countries (PAPAGAIO-Delivery): an individualised randomised controlled trial

PROTOCOL version 2

Funder: National Institute for Health and Care Research, NIHR156828

Principal Investigator:
Professor Andrew Shennan, King's College London

Joint Principal Investigator:
Professor Leandro de Oliveira, Sao Paulo State University

Trial Sponsor: King's College London, Strand, London, WC2R 2LS. Tel: 020 7836 5454

Table of Contents

Introduction

Background

It is estimated that preeclampsia affects 3 – 5% of pregnancies, while suspected preeclampsia affects 10% of women.[1] In the UK, maternal mortality has reduced, such that at its lowest less than one woman per million pregnancies will die from preeclampsia.[2] The contrast to the global context, where preeclampsia is one of the leading causes of maternal mortality, remains one of the starkest avoidable health injustices in the world. Around 30,000 maternal deaths occur each year due to pre-eclampsia, with 70% in Sub-Saharan Africa and 16% in South Asia.[3] Preeclampsia is associated with perinatal mortality; there are an estimated 500,000 fetal and neonatal deaths annually, with 99% occurring in Sub-Saharan Africa and South Asia.[4] Deaths from preeclampsia are avoidable, even in low-income settings, through early identification and instigating timely delivery. Interventions that reduce maternal and perinatal mortality and morbidity are urgently needed. This has been highlighted in the Sustainable Development Goals.

Preeclampsia is defined as hypertension with maternal organ dysfunction, comprising proteinuria, haematological, biochemical, or neurological abnormalities, or uteroplacental dysfunction, evidenced by fetal growth restriction or stillbirth.[5,6] It is a complex and heterogenous syndrome, with a vast spectrum of disease. Diagnosis is challenging in low and middle-income countries (LMICs) due to variable access to blood pressure (BP) equipment, urine dipsticks, blood tests and scans. The disease course is unpredictable and missed diagnosis can have devastating maternal and perinatal consequences.

Placental growth factor testing

The advent of testing for angiogenic biomarkers such as placental growth factor (PlGF) has transformed the ability to identify women at high risk of adverse outcomes in high income settings. Circulating angiogenic factors play a key role in the pathogenesis of preeclampsia, and angiogenic imbalance is more closely associated with the underlying aetiology of preeclampsia, compared to downstream features of disease such as hypertension and proteinuria. Abnormally low concentrations of pro-angiogenic placental growth factor (PlGF) and elevated anti-angiogenic

soluble fms-like tyrosine kinase-1 (sFlt-1) have been identified up to 10 weeks prior to the clinical onset of PE.[7]

There are now commercially available tests for these angiogenic biomarkers, which measure PlGF alone, or the ratio of sFlt-1/PlGF. PlGF has high test performance (area under receiver operator curve (AUROC) 0.87, standard error 0.3) for delivery for confirmed preeclampsia within 14 days, outperforming all currently used diagnostic tests for suspected preeclampsia combined, including BP, proteinuria, or biochemical abnormalities.[8] Normal maternal PlGF concentrations rule out the development of preeclampsia necessitating delivery within 14 days with high negative predictive value (NPV) of 0.98 (95% confidence interval (CI) 0.93 – 0.995). This enables low-risk women to continue with routine surveillance while resource-intense, high-level surveillance can be directed to high-risk women with low PlGF, who have a shorter time to delivery and higher risk of complications. Whole blood and point-of-care capillary blood PlGF testing are now becoming available, which provides immediate results without the need for expensive laboratory infrastructure and can be undertaken in remote and resource-limited settings.

Timing of Delivery in Preeclampsia

International guidelines recommend delivery at 37 weeks' gestation for women with confirmed preeclampsia.[9] Before 34 weeks' gestation, expectant management is advised, as iatrogenic preterm delivery is associated with worse neonatal adverse outcomes (respiratory distress syndrome risk ratio (RR) 2.3, 95% CI 1.39–3.81, necrotising enterocolitis RR 5.54, 95% CI 1.04–29.56).[10]

Recent research has been investigating optimum timing of delivery between 34- and 37-weeks' gestation, to improve outcomes for women and their babies, in high-income and LMIC settings. In the PHOENIX trial, 901 women in the United Kingdom diagnosed with PE between 34- and 36+6-weeks' gestation were randomised to planned early delivery, compared to expectant management (usual care).[11] Planned delivery was associated with reduced adverse maternal outcomes compared to expectant management (65% vs. 75%, adjusted RR 0.86, 95% CI 0.79-0.94, p=0.0005) and an increase in neonatal unit admissions for prematurity, but without other indicators of neonatal morbidity. This trial in a high-income setting reported no stillbirths.

The CRADLE-4 trial compared the same hypothesis (planned delivery compared to expectant management in late preterm preeclampsia) in 565 women in a low- and lower middle-income setting (Zambia and India).[12] Planned delivery was associated with a 75% reduction in stillbirth (RR 0.25, 95% CI 0.07 – 0.87, p=0.03), 100% reduction in antenatal stillbirths (3.3% vs 0%) and reduction in severe maternal hypertension (43.6% vs 52.1%, p=0.03). There were no significant differences in the primary maternal or primary perinatal outcomes (modified miniPIERS composite of adverse maternal outcomes, and neonatal death, stillbirth, or neonatal unit admission > 48 hours). While these results demonstrate planned early delivery is safe in late preterm PE, early delivery in LMICs

in the absence of PE, would likely increase neonatal morbidity so it is vital that an accurate diagnosis is made. Furthermore, larger studies from varied LMIC settings are needed.

The unmet health need

In most resource-limited settings, preeclampsia treatments such as antihypertensives, anticonvulsants and expedited delivery are available; however, difficulties in early detection of women at risk of severe disease, and failure of timely intervention, result in morbidity and mortality. We anticipate that planned early delivery for women with late preterm pre-eclampsia, with accurate diagnosis incorporating point-of-care angiogenic biomarker testing will reduce adverse outcomes in resource poor settings.

95% of preventable maternal deaths occur in LMICs.[13] In high resourced areas, lifetime risk of dying from a maternal cause is 1 in 5400; the risk is more than 100 times higher for a similar woman born in a LMIC setting. There is urgent need for robust studies of planned early delivery for late preterm pre-eclampsia, and its impact on maternal and perinatal morbidity and mortality, particularly in varied resource-poor settings where maternal and fetal surveillance or monitoring are lacking.

Objectives

Primary objective

Evaluate whether PlGF testing and planned early delivery for women diagnosed with late preterm pre-eclampsia, reduces adverse maternal and perinatal outcomes when compared to usual care.

Secondary objectives

- Evaluate whether the intervention reduces stillbirth when compared to usual care.
- Determine if planned early delivery reduces secondary maternal or perinatal adverse outcomes.
- Assess the health resource use and cost-effectiveness of planned early delivery, informed by PlGF testing, compared to usual care.

Trial design

The PAPAGAIO-Delivery trial will be an international, multi-centre, parallel-group, superiority, individually randomised controlled trial. Women between 34- and 37-weeks' gestation will be randomly assigned (1:1) to PlGF testing, or usual care. In the PlGF testing group, women with a PlGF concentration less than 100 pg/ml will be recommended for planned early delivery and women with a normal PlGF concentration above 100 pg/ml recommended for expectant management.

Methods: Participants, interventions, and outcomes

Study setting

The trial will be conducted in around three to five hospitals in each country, in total at around 12 – 20 sites across Sierra Leone, Zambia, India and Brazil.

Eligibility criteria

Pregnant women will be eligible to participate in the randomised trial if they are able to give informed written or thumbprint consent (or assent if < 18years with parental or guardian consent) and fulfil the following inclusion criteria:

1. **Hypertension (sustained blood pressure above 140 or 90 mmHg)**
2. Between 34- and 36^{+6}-weeks' gestation*
3. Singleton live pregnancy

* Gestational age will be determined by ultrasound if available, or by last menstrual period if known, or by presence of fetal movements and fundal height palpation if other methods not available.

Exclusion criteria for randomisation:

- In labour
- Decision to deliver within 48 hours already made (including due to indication for immediate delivery, as defined by WHO guidelines and standard local practice[9])

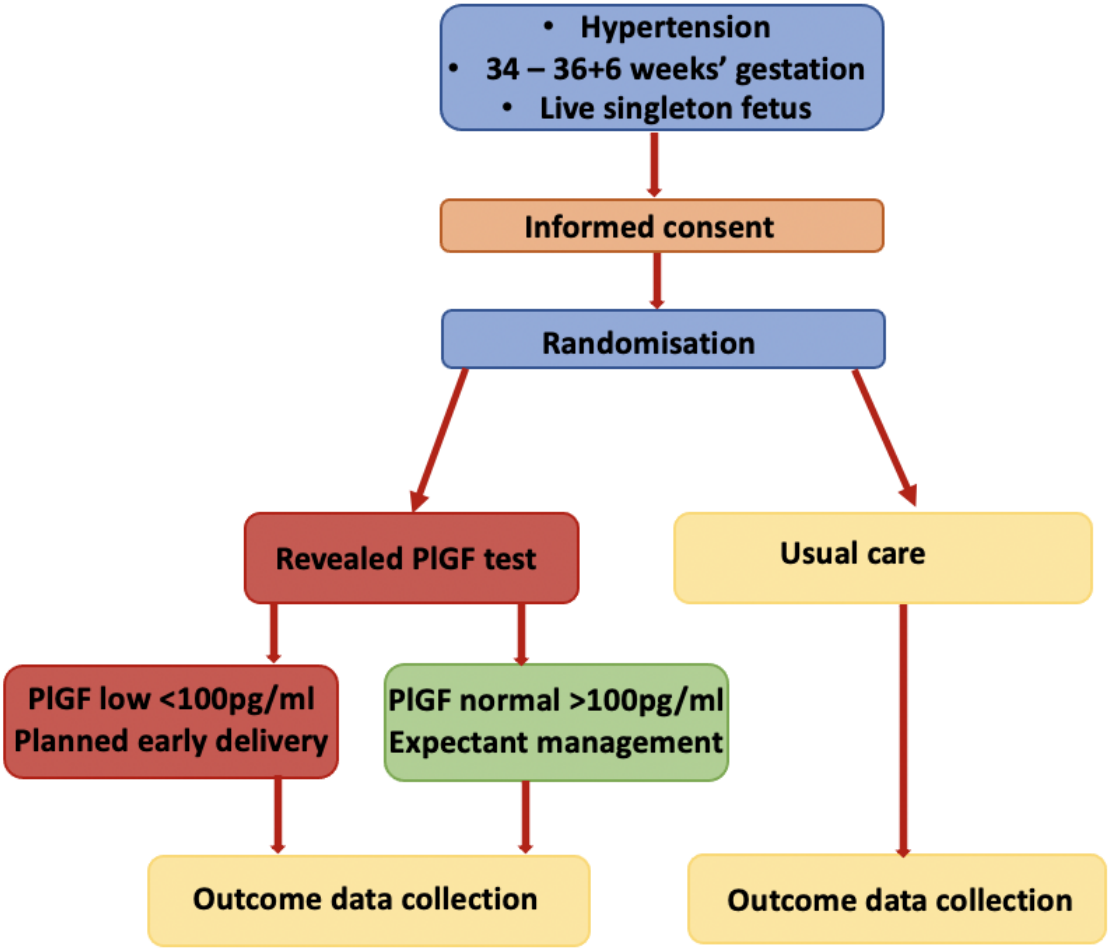

Figure 1. Trial flow diagram

Who will take informed consent?

Participant information infographics and leaflets will be developed in partnership with community engagement specialists and community members in local languages to explain the trial in an accessible manner. Women who meet the inclusion criteria will be approached, by either the clinical or research team, to consider participation. The research team will give a clear verbal explanation of the trial to women meeting the inclusion criteria in her preferred language and will provide the supplementary information media to aid comprehension to trial potential participants and relatives. The team will read the leaflets aloud to the woman if she is unable to read it herself. Women will be given time to ask questions and to consider whether she wishes to participate. Written or thumbprint informed consent will be taken from the woman by a member of the research team on the delegation log and trained in the study protocol.

Additional consent provisions for collection and use of participant data and biological specimens

At participating sites, additional consent will be sought for participation in the PAPAGAIO Biobank and New Test Validation Study (see separate protocols). Participation in these studies will involve testing for preeclampsia biomarkers on novel Point of Care (POC) test devices, and storage of serum, plasma, whole blood, and urine samples in the biobank.

Explanation for the choice of comparators

In the control group, participants will have usual care until either they labour spontaneously or they develop an indication for delivery, as per local or international guidelines. Training on best practice and indications for delivery will be provided to clinical teams at each site, and will be in line with WHO recommendations.[9]

Intervention description

Screening:

Patients presenting with hypertension will be screened for eligibility. If they meet the gestational age requirements, have a live singleton pregnancy, and provide informed consent, they will be offered randomisation to either the intervention or comparator group.

Intervention:

The intervention is PlGF testing, plus planned early delivery for women with an abnormal PlGF concentration (less than 100 pg/ml) or expectant management for women with a normal PlGF concentration (above 100 pg/ml). Planned delivery to be undertaken as soon as is safe and feasible. The target will be to commence delivery within 48 hours from randomisation. The use of antenatal corticosteroids for fetal lung maturity will be at the discretion of the clinician in accordance with local guidelines. Delivery will be through induction of labour according to the local protocol (typically administration of misoprostol) or via caesarean section for women in whom an elective procedure was planned; caesarean section will be an option where indicated.

Criteria for discontinuing or modifying allocated interventions

Any participants that develop preeclampsia with severe features will be offered immediate delivery in accordance with local or international guidelines, regardless of their trial group.

Strategies to improve adherence to interventions

Training events on pre-eclampsia management and PlGF testing, and interpretation will be conducted at all trial sites, prior to the trial commencing and at regular (at least yearly) intervals; co-designed training materials will be developed and distributed. Monitoring visits will ensure that staff are adequately trained in the trial protocol, and that clinical and research staff are trained in

interpreting PlGF-based tests and initiating planned early delivery within 48 hours. Regular monitoring trips will be undertaken to supervise, monitor and audit data collection of primary and secondary outcomes, in addition to real time online data monitoring. Minor protocol non-adherences will be monitored throughout by trained research staff in each site and communicated to the central trial management group.

To facilitate monitoring of adherence to the intervention all participants, regardless of group, will have the time of onset of planned delivery or spontaneous labour recorded following their inclusion to the trial. This will enable identification and investigation of protocol deviations.

Relevant concomitant care permitted or prohibited during the trial

Participants in both groups will receive usual antenatal, intrapartum, and postpartum care in accordance with local guidance.

Provisions for post-trial care

As sponsor, King's College London has specialist insurance policy in place which would operate in the event of any participant suffering harm because of their involvement in the research. Following hospital discharge participants will receive routine postnatal care as provided by their facilities.

Outcomes

Primary outcomes

- Maternal: A composite of severe maternal adverse outcomes relating to pre-eclampsia, as defined by the Pre-eclampsia Delphi consensus[15], and used in other pre-eclampsia studies conducted in LMIC[12,16] with the addition of severe hypertension > 160 mmHg (see box below)

- Perinatal: Perinatal death (stillbirth, early neonatal death within first seven days of life)

Outcome	Definition
Maternal mortality	Maternal death prior to discharge form hospital
Eclampsia	Any episode of eclamptic seizure prior to discharge
Glasgow coma score <13	Based on GCS scoring system
Stroke	Acute neurological event with deficits lasting longer than 48 h
Cortical blindness	Loss of visual acuity in the presence of intact pupillary response to light
Retinal detachment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (RPE; choroid) and is diagnosed by ophthalmological exam
Reversible ischaemic neurologic deficit (RIND)	Cerebral ischaemia lasting longer than 24 h but less than 48 h revealed through clinical examination
Acute renal insufficiency	According to KIDIGO definition
Need for dialysis	Including haemodialysis and peritoneal dialysis, including if dialysis recommended but unavailable
Hepatic Dysfunction	Elevated liver enzymes
Hepatic haematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Positive inotropic support	The use of vasopressors to maintain blood pressure
Postpartum haemorrhage (PPH)	Occurrence of PPH that was more than 1000mls
Placental abruption	Any occurrence of abruption diagnosed clinically or based on placental pathology report
Transfusion of blood products	Includes transfusion of any units of blood products: fresh frozen plasma (FFP), platelets, red blood cells (RBCs), cryoprecipitate (cryo) or whole blood. Includes request for transfusion even if products unavailable at time of request.
Low platelets	Measurement of platelet count recorded as less than 50,000
Myocardial ischaemia/infarction	ECG changes (ST segment elevation or depression) with ischaemic symptoms with or without typical enzyme changes
Pulmonary oedema	Clinical diagnosis with, or without X-ray confirmation.
Severe breathing difficulty	Suspected pulmonary oedema where X-ray confirmation is unavailable may be diagnosed by presence of chest pain or dyspnoea, crackles in the lungs and $SaO_2 < 90\%$
Require > 50% oxygen for greater than 1 h	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 h
Intubation other than for Caesarean section	Intubation may be by endotracheal tube insertion or continuous positive airway pressure
Admission to ICU required	Admission to Intensive Care Unit (or equivalent) required (including if unavailable due to bed availability)

Secondary outcomes

Tested Maternal Outcomes

- Individual components of composite maternal outcome:
    - Maternal mortality
    - Eclampsia
    - Placental abruption
    - Severe hypertension ≥160mmHg
- Time to delivery
- Time to initiation of delivery
- Mode of birth (vaginal, assisted vaginal, caesarean section)
- Postpartum haemorrhage (>1000mls)
- Length of stay

Descriptive Maternal Outcomes

- All remaining individual components of the composite:
    - Stroke
    - Cortical blindness
    - Retinal detachment
    - Pulmonary oedema
    - Acute Kidney injury
    - Liver capsule haematoma/rupture
    - Major post-partum haemorrhage
    - Hepatic dysfunction
    - Platelets <50,000
    - ICU admission
    - Intubation and ventilation (other than for delivery)
    - Glasgow coma score <13
    - Transient ischaemic attack
    - Posterior reversible encephalopathy
    - Positive inotropic support
    - Myocardial infarction/ischaemia
    - Blood oxygen saturation <90%
    - Requirement of ≥50% FiO2 for >1 hour
    - Supplemental oxygen >50% for more than 1 hour
    - Dialysis required
- Use of MgSO4
- Use of steroids
- Use of antihypertensives
- Parenteral infusion of antihypertensives
- PlGF result
- Labour onset (spontaneous, induced or pre-labour Caesarean)

Tested Perinatal Outcomes

- Stillbirth
- Early neonatal death (within 7 days of life)
- Neonatal unit admission
- Neonatal unit admission >48 hours
- Gestational age at delivery
- Birthweight <10th centile (Intergrowth-21)

Perinatal Outcomes

- Late neonatal death (7 – 28 days of life, or up to primary discharge from hospital)
- Respiratory support
- Sepsis
- Neonatal seizures
- Birthweight
- Birthweight <3rd centile (Intergrowth-21)
- Antibiotics given
- APGARs at 1 and 5 minutes
- Need for neonatal resuscitation
- Hypoxic Ischaemic Encephalopathy and grade
- Respiratory distress syndrome
- Supplementary oxygen and duration
- Administration of surfactant
- Hypoglycaemias requiring intervention
- Hypothermia Temp <35.6
- Neonatal jaundice requiring phototherapy
- Necrotising enterocolitis
- Nasogastric feeding required
- Umbilical artery and venous pH
- Abnormal cerebral ultrasound
- Fetal sex

Health resource use outcomes for budget impact analysis:

- Number of POC-PlGF cartridges used
- Wastage of consumables e.g., due to protracted time un-refrigerated
- Number of failed tests

Maternal

- Antenatal outpatient attendances
- Formal ultrasound scans
- Inpatient days

- High dependency unit / Intensive care unit use

Neonatal

- Total days in hospital
- Total days in each level of care (intensive care, high dependency, and special care unit days)

Process indicators for implementation analysis:

Screening and eligibility

- Number of eligible women

Recruitment

- Number of women recruited
- Number/percent receiving PlGF test
- PlGF result recorded in database and in handheld/notes

Delivery of Intervention:

Planned early delivery group

- Time from randomisation to initiation of delivery (target within 48 hours)
- Mode of initiation of delivery (induction, planned Caesarean)

Expectant management group

- Gestational age at delivery
- If delivery before 37 weeks' gestation, indication for delivery

Protocol deviations

- Proportion of planned early delivery group who were still pregnant >96 hours post-randomisation
- Proportion of expectant management group in whom delivery initiated within 48 hours without documented indication for delivery

Participant timeline

Trial Procedures	Screening	Enrolment	At discharge
Confirmation of eligibility (including auscultation of fetal heart rate)	**X**		
Consent		**X**	
Collection of baseline demographic and clinical data (including BP measurement)		**X**	
Randomisation		**X**	
Blood sample for PlGF testing (intervention group only)		**X**	
Initiation of planned early delivery (intervention group only)		**X**	
Completion of post-delivery outcome form			**X**

Sample size

Assuming an event rate of 4.5% for perinatal death[12], a trial of 1194 women would have 90% power to detect a 70% event rate reduction to 1.35% (CRADLE-4 demonstrated a 75% reduction in stillbirth). Assuming 5% loss to follow-up, we will aim to recruit 1254 women, across the 4 sites (315 women at each site).

For the primary composite adverse maternal outcome, a trial of 1042 women would have 90% power to detect an 20% event rate reduction from a baseline of 55%[11,12] to 44%, at an alpha of 0.05 confidence intervals (2-tailed).

Recruitment

Recruitment rate to achieve the target sample size has been based on recruitment to similar studies previously. There will be approximately four participating sites in each country (Sierra Leone, Zambia, India, Brazil). Recruitment rate will be monitored monthly, and there is capacity to include additional sites if needed to reach the target sample size.

To recruit our target of 1260 women within 16 sites in 12 months, we will need to recruit 6.6 women per centre, per month. Recruitment will be continuously monitored. The DMC will conduct a review of the primary outcome event rate at each DMC meeting. If needed, there is potential to increase our number of centres.

Assignment of interventions: allocation

Sequence generation

A secure web-based randomisation facility hosted by OMDA (previously MedSciNet) will manage the randomisation and hold the allocation code. Participants will be allocated at a 1:1 ratio to either the intervention or control group (PlGF testing with planned early delivery and expectant management according to the result, OR usual care respectively). To ensure balance, recruitment will be minimised by parity (0 or ≥ 1), gestational age at randomisation (34+0 – 34+6, 35+0 – 35+6, 36+0 – 36+6). The trial statistician will extensively check the randomisation prior to starting recruitment and at subsequent DMC meetings.

Concealment mechanism

OMDA will ensure that the allocation mechanism is concealed from researchers, clinicians, and participants.

Implementation

Potential participants will be identified by the direct clinical care team. Participants will be enrolled

by members of the research team, trained in recruitment and enrolment, and written informed consent will be taken by personnel on the delegation log trained in the study protocol. The OMDA platform will generate the allocation sequence and will randomise to the planned early delivery or expectant management arm. The research team will inform the direct clinical care team and participants of the outcome of randomisation, and the PlGF test result.

Assignment of interventions: Blinding / masking

Who will be blinded

Due to the trial design, it is not possible to mask the clinical care team, the researchers or the women who participate.

Procedure for unblinding if needed

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes

Data collected will include baseline demographic and pregnancy characteristics at presentation and maternal, birth and neonatal outcomes. Pseudo-anonymised clinical data will be collected by trained research staff until primary hospital discharge of the woman and baby. Most of the outcome data required for the trial are routinely recorded clinical parameters detailed within the patient records. Data collectors will use a combination of handheld paper notes, electronic records, hospital registries and verification with participants to confirm outcomes.

The PlGF result will be recorded by the research team into the database. Additionally, the PlGF readers retain an electronic record of previous results that are stored automatically. These will be verified against those entered on the database.

The central coordinating team will verify outcome data from a minimum of 10% of participants per site. All adverse outcomes will be verified.

All data collectors will receive training prior to commencement of the study regarding how to ensure data quality and accuracy, and how to maintain data protection.

Please also see the data management plan.

Plans to promote participant retention and complete follow-up

We will ensure timely outcome data collection, aiming to collect outcomes within two weeks of delivery. To facilitate this, a record of the estimated delivery date (EDD) of each participant will be made, and the clinical records of participants will be checked weekly following their EDD to identify delivery times. We will ensure close collaboration with neonatal units for follow up of perinatal outcomes. We will ensure that close relationships exist between the research teams and the referral units related to their clinical site. In the instance that a participant is either referred for, or choses, delivery elsewhere, the research teams will aim to follow up the outcomes at that site. The contact details of participants and their next of kin will be taken at recruitment, and with the participants prior consent, we will contact them following their delivery should the research teams require further information to record full outcomes (such as confirming date or location of delivery).

For participants that deviate from intervention protocols we will aim to capture full outcome data.

Data management

During the study, the data will be stored on a secure OMDA database. OMDA Servers are stored in locked rooms, with system monitoring 24 hours a day, physical surveillance and surveillance cameras. A tape backup system is used for backing up the database.

An OMDA password protected account is required to access to the encrypted database. Accounts will only be issued to the data collectors and other relevant members of the trial co-ordinating team. Data collectors will only have data entry rights. Data collectors will be provided with password protected study laptops. Strong password policies including the password length and complexity restrictions will be enforced. All database back-ups will also be encrypted.

Source data, where paper -based, will be kept in files in secure areas at each central site. Only healthcare providers involved in participants' care, data collectors, the trial co-ordinators and authorised auditors will have access to these. All paper documents will be stored securely and kept in confidence in compliance with local and international guidelines, including the Data Protection Act (2018).

Contemporaneous data cleaning will be conducted. All variables will be summarized and reviewed for distribution, central tendency and spread, using standard tabular and graphical methods. Verification against clinical records will be performed for values that are outlying or clinically implausible. The dataset will be locked for analysis only when all data queries have been resolved.

The study database will remain live for one year following completion of the study. An inactive copy of the database will then be kept on the KCL server for 25 years under the responsibility of the unit statistician, regulated by the Joint Clinical Trials Office, as per KCL and NIHR policy.

Please see the data management plan for further details.

Confidentiality

Data will be pseudonymised at collection. All data will be directly entered onto the secure, online database (OMDA). Individual participant data will be recorded under a unique study identifier created for each participant, and no identifying information will be entered into the clinical study database.

Personal contact information for the participants (name, DOB, telephone number and Next – of – kin telephone number) will be collected from each participant to enable later follow up. This will be kept on a secure local database (password protected and encrypted) with written consent from the study participants. This local database will only be accessible by the local data collectors from password protected trial computers.

The link between the participants' personal identifying information and their unique Participant ID will be stored securely under lock and key and in a password protected computer. This will be available to designated and authorised members of the study team during the period of study participation only. After this period this link between participants' IDs and to identifiers will be further controlled and only available to the Principal Investigator.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

A whole blood sample will be collected at enrolment from all participants. The blood sample will be obtained by either venepuncture or fingerprick (according to the manufacturer's instructions) and processed immediately at the bedside on the point of care PlGF testing device. The results will be recorded in the clinical notes and on the study database and the clinical care team will be directly informed.

If the participant has consented to be co-recruited to the PAPAGAIO Biobank or New Test Validation Study, any remaining sample will be used for the purposes outlined in the relevant study protocols/consent forms. If the participant is only recruited to PAPAGAIO-Delivery, any remaining sample will be disposed of.

Statistical methods

Statistical methods for primary and secondary outcomes

Analysis will follow the intention-to-treat principle. Women in the usual care group will frequently be delivered prior to 37 weeks of gestation due to clinical need and this will not be considered a protocol deviation. Both an intention-to-treat and per-protocol analysis will be performed for maternal and perinatal outcomes. The per-protocol analysis will exclude babies of women who do

not receive the allocated intervention as per protocol. All outcomes will be analysed adjusting for minimisation factors at randomisation where possible. Binary outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios with associated confidence intervals (CI), with unadjusted risk ratios or odds ratios if there is no convergence. Continuous outcomes will be analysed using linear regression models. Results will be presented as differences in means with associated confidence intervals (CIs). The consistency of the effect of planned delivery vs. expectant management across subgroups will be assessed using a likelihood ratio test for interaction.

Please see the Statistical Analysis Plan for further details.

Interim analyses

An independent Data Monitoring Committee (DMC) will be formed to review the progress of the trial. Confidential interim analyses will be provided to the DMC, at the request of its Chair. The committee will consider the results for the primary endpoints in both trial arms and all Serious Unexpected Adverse Events and conclude whether the trial can ethically continue. If there is overwhelming evidence (P<0.001) favouring one intervention, the DMC may advise that the trial will be stopped in accordance with the Peto principle.[18]

The research teams will only be informed of the results of the interim analysis if trial modifications or cessation are advised by the DMC. In the event of concerns about the study, the relevant party may contact the DMC.

Methods for additional analyses (e.g., subgroup analyses)

Pre-specified subgroup analyses will be performed for gestation at randomisation and country. These analyses will include a statistical test of interaction and, where appropriate, results will be presented as relative risks with confidence intervals. There will also be a prespecified sensitivity analysis on the primary outcome excluding women and infants assigned to the planned delivery group, for whom initiation of delivery was more than 96 hours post randomisation.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Participants will be analysed according to their original randomisation arm, in line with the intention to treat principle when analysing maternal outcomes. Both an intention-to-treat and per-protocol analysis will be performed for perinatal outcomes. The per-protocol analysis will exclude babies of women who do not receive the allocated intervention as per protocol

Missing data will be described and if there are > 5% missing primary outcome data, sensitivity analysis will be conducted using multiple imputation methods to impute missing data, assuming that the outcome is not linked to the reason for being lost to follow-up (i.e. missing at random).

Plans to give access to the full protocol, participant level-data and statistical code

The protocol will be published in an open-access journal. Access to the statistical code and the fully anonymised dataset will be granted on request, subject to the relevant approvals.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

Co-ordinating Centre

The trial co-ordinating team will be based at KCL, which will be the trial co-ordinating centre. The trial coordinating centre will be responsible for the general management of the trial in partnership with the site PIs, including staff training and site liaison. The coordinating centre will also conduct data monitoring and statistical analyses.

Project Management Group (PMG)

The PMG will provide general supervision for the trial. The PMG will meet on a monthly basis, at a minimum, and will receive updates from local PIs, the trial co-ordinator and the trial statistician.

The PMG will consist of:

- Local PIs
- Local trial managers
- Trial coordinators
- Trial statistician

Co-Investigators Group (CIG)

The Co-Investigators' Group (CIG) will be formed of members of the co-applicant group and key collaborators. They will be responsible for strategic oversight and planning. Initially, the CIG will meet every three months, and every four to six months thereafter.

Trial Steering Committee (TSC)

The TSC will provide overall supervision of the trial. They will monitor the conduct and progress of the trial and ensure the scientific credibility. The TSC will consider any DMC recommendations and will ultimately be responsible for the decision for early interruption of the trial.

There will be an independent chair and at least two other independent members, in addition to the Principle Investigators. Observers can be present at the agreement of the TSC chair. The trial coordinating team will provide secretariat function to the TSC. The TSC will agree a TSC charter at the first meeting, documenting how the committee will operate.

Composition of the data monitoring committee, its role and reporting structure

The members of the DMC will be independent to both the TSC and Investigator team and will include a statistician and a clinical expert. The DMC will review the progress of the trial on an annual basis, more frequently if required, and will review the results of the interim analysis and all SAEs. They will advise the TSC on the conduct of the trial where appropriate. The DMC will agree a Charter at the first meeting which will outline the schedule and agenda for its reviews.

Adverse event reporting and harms

An 'adverse event' is defined as any unfavourable or unexpected medical occurrence that happens to a participant during study participation. It may not have a causal relationship with the intervention. A high incidence of adverse events is expected in this participant population, consequently only those identified as 'serious and unexpected' will be recorded for the trial.

A 'serious adverse event' (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly/birth defect

'Expected SAEs' are reasonably expected in the participant population as part of routine management. They will be recorded as clinical outcomes but will not be reported as SAEs. The following are considered expected SAEs among women with preeclampsia and their babies:

Expected Maternal SAEs	• Hepatic dysfunction • Hepatic haematoma or rupture • Coma/impaired consciousness (Glasgov coma score <13) • Cortical blindness • Reversible ischaemic neurological defic • Retinal detachment • Acute renal insufficiency or failure • Postpartum haemorrhage requiring transfusion or hysterectomy • Eclampsia • Maternal stroke • Maternal death •	• Platelet count <50,000 • Severe uncontrolled hypertension • Myocardial ischaemia/infarction • Severe breathing difficulty • Pulmonary oedema • Sepsis • Admission to hospital for pregnancy-related monitoring, or monitoring for other medical or psychiatric condition in pregnancy • Admission to high dependency unit or intensive care unit for an expected complication

Expected Infant SAEs	• NNU admission • Congenital anomaly • Low birth weight • Reversed end diastolic flow • Requirement for supplemental oxygen or ventilation support • Stillbirth • Neonatal death	• Intraventricular haemorrhage • Sepsis • Necrotising enterocolitis • Seizures • Encephalopathy • Hypoglycaemia

An 'unexpected SAE' is any SAE not detailed in the list above. All Unexpected SAEs will be recorded and reported by the site PI to the coordinating team and study PIs (AHS and LdO) within 24 hours of the site PI becoming aware of the event. Details should be recorded on a SAE form and sent by email. If an SAE is 'related' (resulted from administration of the research procedures) and 'unexpected' in relation to those procedures, it should be reported to the Research Ethics Committee. Reports of related and unexpected SAEs should be submitted within 15 working days of the CIs becoming aware of the event, using the relevant form. All SAEs will be reviewed by the DMC.

Frequency and plans for auditing trial conduct

The PIs will ensure that adequate quality and number of monitoring activities are conducted by the study team. The central coordinating team will verify outcome data from a minimum of 10% of participants per site. All adverse outcomes will be verified.
This will include routine auditing of study documents to verify adherence to the protocol and consenting procedures, as well as regular data quality assurance. Where indicated, corrective measures and/or top-up training will be implemented. The PI will inform the Sponsor should concerns arise from monitoring activities, and/or if there are problems with oversight/monitoring. The DMC will monitor protocol adherence as part of its remit.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

Any modifications to the protocol will be shared with relevant parties via email. A secure KCL password-protected share point will be accessible to the investigators and research teams, the most up to date versions of the protocol and other study documentation will be kept there. Study documents will also be available on the password-protected trial database.

Dissemination plans

All publications will be shared with the TSC for review prior to submission. A writing committee drawn from the co-investigators, study coordinators and others substantially involved in execution, analysis and interpretation will be named authors on the principal publications if they meet standardised authorship criteria (http://www.icmje.org). Authorship will be equitable, across participating countries.
Findings will be presented at specialist maternal health international conferences, and be submitted for publication in high-impact, peer-reviewed scientific journals. There are no commercial or intellectual rights issues that would delay publication of results.

To reach a non-specialist audience, general dissemination of the results will be achieved through publication of summary findings in a style that is understandable and useable for all stakeholders. These may be in the format of short reports, press articles, bulletins and mixed-media including infographics and videos. Press releases will be coordinated by the lead coordinating centers in each country. Results will be made available on the trial website and social media channels, and on those of relevant partners such as KCL, NIHR, and patient support groups.

The majority of participants may not speak English as a first language, and many may have limited literacy and access to technology, therefore extensive efforts will be made to disseminate key findings in local languages via accessible sources, such as at community meetings, and on radio or television bulletins.

Discussion

The trial will be conducted in diverse settings, in several languages, with varying availability of resources. Consequently, efforts will be made to ensure consistency of trial delivery across the sites, whilst also offering flexibility to ensure the conduct of the trial is context specific. The training programme and materials will be developed as part of Prepare for PAPAGAIO in partnership with local stakeholders and will be piloted to ensure their feasibility and acceptability. Local research teams will receive standardised training and refresher sessions on the trial protocol but will be encouraged to consider innovative and adaptive methods for delivery within the confines of their local setting. There will be open communication channels between the research teams at different sites with the opportunity to share learnings.

Trial status

Protocol version: 1
Date recruitment to start: approx. 01/11/2025
Date recruitment to finish: approx. 01/05/2027

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
APEC	Action on pre-Eclampsia
CI	Chief Investigator
CIG	Co-Investigator Group
CT	Clinical Trial
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICU	Intensive care Unit
ISRCTN	International Standard Randomised Controlled Trial Number
ISSHP	International Society for the Study of Hypertension in Pregnancy
KCL	King's College London
LMIC	Low- and middle-income countries
NIHR	National Institute for Health Research
NNU	Neonatal Unit
PI	Principal Investigator
PIL	Participant Information Leaflet
PlGF	Placental Growth Factor
PMG	Project management Group
POC	Point of care
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMW	Research Midwife
SAE	Serious Adverse Event
TMG	Trial Management Group
TSC	Trial Steering Committee

Declarations

Acknowledgements

The success of the trial depends on many midwives, obstetricians, research staff and participants. Credit for the trial findings will be given to all those who have collaborated and participated in the clinical trial, including all local coordinators and collaborators, members of trial committees and clinical trial staff.

Authors' contributions

AS and LdO are Chief Investigators and conceived the study. Draft protocol prepared by AH & LS.

Co-investigators provided comments on the initial draft and subsequent revisions. All authors have read and approved the final manuscript.

Funding

This trial is funded by the National Institute for Health and Care Research (project reference **NIHR156828**). The study sponsor and funder have had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Availability of data and materials

Requests for the final dataset can be made through the chief investigator in accordance with the data-sharing policies of King's College London, with input from the co-investigator group where applicable.

Ethics approval and consent to participate

Trial Conduct will be according to the principles of the Declaration of Helsinki (October 2024) and in full compliance with Good Clinical Practice and all applicable regulatory requirements. Copies of the protocol, participant information leaflet and informed consent form will be approved by national or institutional research ethics committees in the UK and each participating site country:

- King's College London:
- University of Zambia:
- India:
- Brazil:
- Sierra Leone:

The chief investigator or delegate will submit any substantial amendments to the research ethics committees. All protocol modifications will be communicated promptly following approval. Written informed consent will be obtained by the study team.

Consent for publication

Not applicable for the protocol. All participants will complete a consent form confirming they agree for results of the trial to be published. An example consent form can be shared upon request.

Competing interests

All PAPAGAIO co-investigators will declare competing interests or affiliations. Members of the TSC and DMC committees, and any observers to the meetings, will be required to declare any competing interests they may have prior to participating in the meetings, as documented with the charters.

References

1. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet*. Mar 2016;387(10022):999-1011. doi:10.1016/S0140-6736(15)00070-7
2. Shennan AH, Green M, Chappell LC. Maternal deaths in the UK: pre-eclampsia deaths are avoidable. *Lancet*. 02 2017;389(10069):582-584. doi:10.1016/S0140-6736(17)30184-8
3. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. Sep 2014;384(9947):980-1004. doi:10.1016/S0140-6736(14)60696-6
4. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. Jun 2009;33(3):130-7. doi:10.1053/j.semperi.2009.02.010
5. Brown MA, Magee LA, Kenny LC, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension*. 07 2018;72(1):24-43. doi:10.1161/HYPERTENSIONAHA.117.10803
6. Hypertension in Pregnancy: diagnosis and management. (2019).
7. Chaiworapongsa T, Romero R, Kim YM, et al. Plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated prior to the clinical diagnosis of pre-eclampsia. *J Matern Fetal Neonatal Med*. Jan 2005;17(1):3-18. doi:10.1080/14767050400028816
8. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation*. Nov 5 2013;128(19):2121-31. doi:10.1161/CIRCULATIONAHA.113.003215
9. WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. http://apps.who.int/iris/bitstream/handle/10665/44703/9789241548335_eng.pdf?sequence=1 (2021. Accessed 11th January 2023.).
10. Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. *Cochrane Database Syst Rev*. Oct 05 2018;10(10):CD003106. doi:10.1002/14651858.CD003106.pub3
11. Chappell LC, Brocklehurst P, Green ME, et al. Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. *Lancet*. 09 2019;394(10204):1181-1190. doi:10.1016/S0140-6736(19)31963-4
12. Beardmore-Gray A, Vousden N, Seed PT, et al. Planned delivery or expectant management for late preterm pre-eclampsia in low-income and middle-income countries (CRADLE-4): a multicentre, open-label, randomised controlled trial. *Lancet*. Jun 29 2023;doi:10.1016/S0140-6736(23)00688-8
13. Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and
UNDESA/Population Division (Licence: CC BY-NC-SA 3.0 IGO) (2023).
14. Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. Mar 2022;27:148-169. doi:10.1016/j.preghy.2021.09.008
15. Duffy J, Cairns AE, Richards-Doran D, et al. A core outcome set for pre-eclampsia research: an international consensus development study. *BJOG*. Nov 2020;127(12):1516-1526. doi:10.1111/1471-0528.16319
16. Payne BA, Hutcheon JA, Ansermino JM, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS

(Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. *PLoS Med*. Jan 2014;11(1):e1001589. doi:10.1371/journal.pmed.1001589
17. Webbe JWH, Duffy JMN, Afonso E, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. *Arch Dis Child Fetal Neonatal Ed*. Jul 2020;105(4):425-431. doi:10.1136/archdischild-2019-317501
18. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer*. Dec 1976;34(6):585-612. doi:10.1038/bjc.1976.220