Title	First-trimester Placental Ultrasound Study (First PLUS)
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Funder	National Institute for Health Research (NIHR) Artificial Intelligence in Health and Care Award

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APPROVALS

Job Title	Name	Signature
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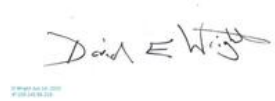
Lead Medical Statistician	Professor David Wright	
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ISSUE CONTROL

Issue	Paragraph	Details	Reason	Date/Initial
1.0	All	New document from all collaborators	Finalised version	10Dec2021

Distribution: Controlled documents are stored electronically on the company SharePoint server.

ABBREVIATIONS

AE	Adverse Event
AI	Artificial Intelligence
CI	Chief Investigator
FGR	Fetal Growth Restriction
FMF	The Fetal Medicine Foundation
GCP	Good Clinical Practice
ICF	Informed Consent Form
NHS	National Health Service
NHSLTP	NHS Long Term Plan
PlGF	Placental Growth Factor
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PAPP-A	Pregnancy associated plasma protein A
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure
UtAD	Uterine Artery Doppler
UtADPI	Uterine Artery Doppler Pulsatility Index
Sv3D-FMBV	Single Vessel three-dimensional Fractional Moving Blood Volume

SYNOPSIS

Investigation Title	First-trimester Placental Ultrasound Study (First PLUS): an observational cohort study to assess the clinical utility of the OxNNet Toolkit for the prediction of adverse pregnancy outcomes.
Internal Ref. No.	CIO-53
Investigation Design	Prospective, Observational, Cohort Study
Investigation Participants	Women 18 years of age or older who have: • A singleton pregnancy • A live fetus at 11^{+0} to 13^{+6} weeks • Pregnancies with no major defects identified during 11^{+0} to 13^{+6} week scan • Full capacity to provide informed consent • Able to understand written and/or verbal English (via translator is acceptable)
Sample Size	4000
Recruitment Period	12 months
Primary Objective	To assess the ability of first-trimester OxNNet generated placental metrics, alone and in combination with other measures, to predict fetal growth restriction (FGR)
Secondary Objectives	• To assess the ability of first-trimester OxNNet generated placental metrics to predict pre-eclampsia • To assess the ability of first-trimester OxNNet generated placental metrics to predict other adverse pregnancy outcomes • To assess the performance of sv3-DFMBV in prediction of adverse pregnancy outcomes compared to the standard measure of UtADPI
Primary Outcome	Fetal Growth Restriction (FGR)
Secondary Outcomes	• Small for gestational age (SGA) • Pre-eclampsia (with, and without, severe features) • Gestational hypertension • Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome • Eclampsia • Gestational diabetes • Preterm birth • Miscarriage • Stillbirth • Neonatal death • Neonatal morbidity
Investigation Procedures	• 3D Ultrasound • Placental Growth Factor (PlGF) blood biomarker

BACKGROUND AND RATIONALE

Unmet Need

In the UK 8 babies/day are stillborn(1) leaving families devastated and costing the NHS an average of £4191 for each lost baby (>£12 million/year)(2). The greatest risk factor for stillbirth is fetal growth restriction (FGR), usually secondary to sub-optimal placentation(3). If they survive, a baby with FGR will usually require a prolonged stay on neonatal ITU costing around £1445/day/baby(4). With >42,000 babies/year born growth restricted, their first days of life place a considerable financial burden on the NHS (conservative estimate of >£61 million/year).

Current Screening

The current methods to assign risk of FGR early in pregnancy are based on maternal history and clinician judgement alone. These perform badly(5) and many women deemed 'low-risk' are unaware their baby is failing to thrive until they present with a stillbirth. If stratified as 'high-risk', women receive serial growth scans with the aim of delivery before in utero demise occurs(5). However, many 'high-risk' women deliver well-grown, healthy babies after a pregnancy riddled with anxiety(5).

A reliable, cost-effective first-trimester screening method for FGR is desperately needed. This would not only improve pregnancy outcomes but decrease unnecessary stress for the women undergoing increased surveillance for no clinical benefit. The NHS Long Term Plan (NHSLTP) aims to reduce stillbirths by 50%. Robust risk assignment enabling targeted monitoring and timely delivery would be a major step towards achieving this reduction.

The Proposed Solution

Using deep learning and an exceptionally large (n=2393) 'ground-truth' dataset, Oxford University has developed, validated and patented a novel, multi-class, 3D fully convolutional neural network (OxNNET)(6, 7). This can automatically identify, and successfully segment, the placenta within a 3D-US image, and then estimate:

1. placental morphology (size, surface area, shape etc.)
2. placental/uterine perfusion.(8, 9)

These innovations have been combined with other novel imaging tools (such as automated artefact removal) in 'user friendly' software to generate the **OxNNet Toolkit**.

We propose to generate a multifactorial FGR risk-prediction algorithm based on **OxNNet Toolkit** derived placental metrics, in combination with other known risk factors. This will provide the much needed first-trimester, population-based screening test for risk of FGR.

Short term future benefit to patients

The clinical adoption of the **OxNNet Toolkit** aims to provide the currently missing, reliable ultrasound markers for a multi-factorial first-trimester screening test to identify those women at high risk of FGR. This will ensure increased operational efficiency by targeting NHS ultrasound resources towards the highest risk women leading to increased diagnosis of FGR and timely delivery before a stillbirth occurs. Also, by not 'medicalising' low-risk women incorrectly stratified as high-risk using the current inaccurate methods, parental anxiety (often leading to multiple unnecessary presentations to antenatal staff) and over-treatment (including early induction of labour) will be reduced(5).

Long term future benefit to patients

With the development of a reliable screening test, the possibility of designing clinical trials for interventions to prevent FGR becomes a reality. These are currently extremely difficult to run because of the low confidence in how women should be stratified, which pushes up the sample size and therefore costs, decreasing incentives to test possible interventions.

Being born growth-restricted increases the baby's risk of obesity, type II diabetes & cardiovascular disease in adulthood(10-12). Therefore, any therapy which can improve placentation and prevent FGR from occurring in the first place will not only reduce stillbirth but also have significant long-term health benefits for the baby. This is in alignment with the aims of the NHSLTP to reduce the incidence of these chronic conditions.

A recent randomised controlled trial (RCT) demonstrated a reduction in incidence of pre-eclampsia when aspirin was given to women in the first-trimester who were deemed to be at high-risk using a multi-factorial screening tool(13). This tool used the ultrasound measurement of the uterine artery Doppler (UtAD) waveform as the placental assessment part of the algorithm. The UtAD waveform however, is only a surrogate marker for placentation and it is very difficult to measure in the first-trimester. As the UtAD waveform value is highly sampling site dependent, there is significant potential for human error despite training and prescriptive measurement protocols(14, 15). Therefore, the performance of that screening tool was relatively poor, so the trial was not adequately powered to examine secondary outcomes such as FGR.

Our pilot data demonstrates that measuring the vasculature of the utero-placental interface (the actual site of the underlying pathology) can predict FGR where the UtAD waveform fails to do so(16), and distinguishes between pregnancies at risk of pre-eclampsia and those at risk of FGR(17). Also as estimation of the OxNNet metrics is fully automated the human error introduced by the highly operator dependent UtAD waveform measurement is also eliminated. Therefore, we propose that using the OxNNet Toolkit derived placental metrics for the multifactorial algorithm will not only improve the algorithm's prediction of pre-eclampsia but also provide a screening test for FGR.

If the OxNNet Toolkit is proven to provide the anticipated robust risk-stratification for FGR, clinical trials of novel therapies will become possible as they will be appropriately powered with a smaller cohort. Consequently, currently promising therapies, such as sildenafil(18) and/or beetroot extract(19), can be appropriately trialled. These promote vasodilation, and animal studies suggest that if given whilst the placenta is still developing (<20 weeks', well before FGR becomes apparent), they improve placental implantation and prevent FGR from occurring in the first place(20). This would not only reduce the number of stillbirths but improve the life-long health of the individual by reducing their risk of diabetes and cardiovascular disease(10-12).

Potential cost savings to the NHS

If clinical efficacy is proven, instigating the screening test should have minimal cost implications as it will be performed at the same time as the routinely offered dating scan. Therefore, does not require any additional appointments or extra ultrasound scans. The other risk factors required for the multi-factorial test are already routinely collected either at booking (e.g., maternal history) or for the 'combined test' for aneuploidy (e.g., serum PAPP-A). Although a formal healthcare economic evaluation is needed (application to a separate funding body is underway for a healthcare economics study), there is a prospect of savings from reducing the number of unnecessary ultrasound scans and antenatal appointments as well as the estimated £4191 per stillbirth prevented(2).

OBJECTIVES AND OUTCOME MEASURES

Primary Objective	Primary Outcome Measures
To assess the ability of first-trimester OxNNet generated placental metrics, alone and in combination with other measures, to predict fetal growth restriction (FGR)	Fetal Growth restriction (FGR) defined according to the ISUOG Delphi consensus guidelines for diagnosis of FGR(21)
Secondary Objectives	**Secondary Outcome Measures**
To assess the ability of first-trimester OxNNet generated placental metrics, alone and in combination with other measures, to predict the following outcomes	
• Small for Gestational Age (SGA)	• <10 centile on population-based centiles • <10th centile on customised centiles

• Pre-eclampsia (with, and without, severe features)	• Defined by the ACOG guidelines for hypertensive disorders of pregnancy(22)
	  ○ Pre-term pre-eclampsia (delivery <37 weeks)
	  ○ Late onset pre-eclampsia (delivery ≥37 weeks)

• Gestational hypertension (PIH)	• Defined by the ACOG guidelines for hypertensive disorders of pregnancy(22)
	  ○ Pre-term gestational hypertension (delivery <37 weeks)
	  ○ Late onset gestational hypertension (delivery ≥37 weeks)

• Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome	• Defined by the ACOG guidelines for hypertensive disorders of pregnancy(22)
	  ○ Pre-term HELLP (delivery <37 weeks)
	  ○ Late onset HELLP (delivery ≥37 weeks)
	Pre-term pre-eclampsia (delivery <37 weeks)

• Eclampsia	• Defined by the ACOG guidelines for hypertensive disorders of pregnancy(22)
	  ○ Pre-term eclampsia (delivery <37 weeks)
	  ○ Late onset eclampsia (delivery ≥37 weeks)

• Gestational diabetes	• Defined as fasting plasma glucose level ≥5.6 mmol/L and/or 2-h plasma glucose level ≥7.8 mmol/L after ingestion of 75g oral glucose.
• Preterm birth	• Birth ≥24^{+0} weeks <37^{+0} weeks
• Miscarriage	• Live fetus at the first-trimester ultrasound scan but subsequent *in utero* fetal death or delivery <24^{+0} weeks
• Stillbirth	• Baby born with no signs of life at ≥24^{+0} weeks' gestation
• Neonatal death	• Baby born alive but dies within the first 28 days of life

• **Neonatal morbidity**	• Neonatal intensive care unit admission and length of stay • Neonatal ventilation – defined as need of positive pressure (CPAP, NCPAP or intubation) • Respiratory distress syndrome - defined as need of ventilation with or without surfactant • Intraventricular haemorrhage (IVH) grade II or above – defined as bleeding into the ventricles • Neonatal sepsis confirmed bacteraemia in cultures • Anaemia - defined as low haemoglobin and / or haematocrit requiring blood transfusion • Necrotizing enterocolitis requiring surgical intervention

STUDY DESIGN

Study Description

First PLUS is a prospective, observational, cohort study which will recruit 4000 unselected women who attend their first-trimester pregnancy scan at the Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital NHS Foundation Trust, London, UK.

Participant involvement is through a single study visit involving the collection of participant demographics and routine medical history, an additional research ultrasound scan, which will take place at the same time as a participant's routine first-trimester scan and an additional blood test (Placental Growth Factor – PlGF).

The research scan will occur at the end of the routine ultrasound scan and will take an additional 3-5 minutes on top of the routine clinic visit. Placental Growth Factor (PlGF) will be measured from residual blood obtained from a sample taken as part of routine clinical care. No additional blood samples will be required as part of this study. All participants will also be followed up until their pregnancy is completed and the outcome will be recorded from their routine pregnancy records.

Consented participants will be asked to partake in the following study activities to obtain the relevant data to achieve the study objectives:

Visit	Time	Visit Details
Visit 1 (in person)	11^{+0} and 13^{+6} weeks of pregnancy *During routine first-trimester ultrasound appointment*	• Confirm eligibility • Obtain informed consent • Record participant demographics and routinely collected medical history • Receive additional ultrasound scan • PlGF blood test (*using sample obtained as routine care*)
Follow up (remote)*	End of Pregnancy	• Record pregnancy outcome from routine pregnancy records

**Outcome of pregnancy will be recorded from routine pregnancy records and no physical follow up visit will be required from study participants*

Study Setting

First PLUS is a single centre study, recruiting participants at the Harris Birthright Centre for Fetal Medicine, Kings College Hospital NHS Foundation Trust. The Harris Birthright Centre provides ultrasound scanning for all the women booked at King's College Hospital for their pregnancy care. All women attending for their routine first trimester ultrasound scan will be assessed for eligibility and will be invited to participate in this study. The routine clinical visit involves a fetal ultrasound scan and measurement of maternal serum PAPP-A and HCG as part of screening for trisomies 21, 18 and 13. Women agreeing to take part in the study, will have an additional ultrasound assessment of the placenta and an additional blood test for PLGF which will be done from the residual blood taken as part of the screening test for trisomies.

Investigation Participants

Every woman, 18 years of age or older, who attends for their first-trimester scan at the Harris Birthright Centre will be invited to take part and screened against the inclusion criteria. They may be subsequently excluded if later testing (including the 11^{+0} to 13^{+6} week scan) demonstrates any of the exclusion criteria (which will not be known at the point of recruitment).

Inclusion criteria

- Pregnant
- 18 years of age, or older
- Presenting for first-trimester combined test screening between 11^{+0} and 13^{+6} weeks of pregnancy
- Participant is willing and able to give informed consent for participation in the investigation.
- Able to understand written or verbal English and able to access methods of translation.
- In the opinion of the investigator, the participant is not at risk or under stress or limited in their ability to participate in the study activities.

Exclusion Criteria

- Participant with a multiple pregnancy (more than one viable fetus) discovered at the scan
- Participant with a non-viable pregnancy discovered at the scan (no detectable heartbeat)
- Pregnancies with major defects identified during 11^{+0} to13^{+6} week scan
- Any pregnancy subsequently found to be chromosomally abnormal as a result of either prenatal or postnatal testing

Sample size

Based on recent recommendations[21] and making conservative assumptions, approximately 2100 cases should be sufficient to develop a multivariable model with 20 predictors and a rare outcome (2%). We intend to collect 4000 cases to ensure enough cases of FGR (3-5%) and pre-eclampsia (1-2%).

If a participant is deemed as ineligible as per the exclusion criteria at any point during the study, the participant will be withdrawn fully from the study. All associated data will be withdrawn, will not undergo analysis and will not contribute to the sample size.

STUDY PROCEDURES

Screening and Recruitment

All women invited to attend the Fetal Medicine Foundation for their first-trimester screening scan will be sent the Patient Information Leaflet (PIL) with their routine appointment letter.

When women attend for their routine appointment, their eligibility will be ascertained by a member of the local clinical research team, they will be offered another PIL and an opportunity to discuss the details of the study. All participants will be given the time to consider the study and will have an opportunity to discuss their involvement with an investigator prior to the informed consent process.

Informed Consent

The Participant Information Leaflet/Informed Consent Form will state:

- the nature of the study
- a participant's involvement
- implications and constraints of the protocol
- risks involved in taking part
- that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give a reason for withdrawal.

The participant must confirm eligibility for the study with a member of the local clinical research team. The potential participant will be allowed as much time as they need to ask any questions and confirm their full understanding of the study. Once they are happy to proceed, Informed Consent will be obtained by a suitably qualified and appropriately delegated member of the local clinical research team by means of participant dated signature on the latest approved version of the Informed Consent Form (ICF). The ICF will also include the dated signature of the local clinical study team member who presented and obtained the Informed Consent. This will be completed in person during their first study visit. The Informed Consent Form shall be signed before any study specific procedures are performed. The Informed Consent process will adhere to ICH GCP guidelines.

A copy of the signed ICF will be given to the participant and the original signed form will be retained at the study site.

Study Visits

Participants will be required to attend a single study visit which will take place at the same time as their routine 11^{+0} – 13^{+6} week first trimester scan. The following activities will take place during the study visit:

Activities	Visit 1 (Routine first-trimester ultrasound scan appointment)	Follow up
Eligibility check	X	
Informed Consent	X	
Demographics & Medical History	X	
3D Ultrasound	X	
Placental Growth Factor (PlGF) blood biomarker	X	
Pregnancy Outcome		X

Demographics & Medical history (~30 min):

The clinical research team will obtain a full self-reported medical history from the participant including any medication that they are currently taking and details of their pregnancy. Standard demographic data (e.g. ethnicity), as collected routinely, will also be obtained either as reported by the participant or from pregnancy records.

Scan Protocol (~3-4min):

All participants will undergo a standardised 3D ultrasound imaging research protocol, in addition to their routine scan, to assess their placenta. Participants will be asked for their consent to have images stored at the time of initial consent. The ultrasound scan is not painful or risky and the additional scan time to complete the research protocol will be no longer than 4 minutes.

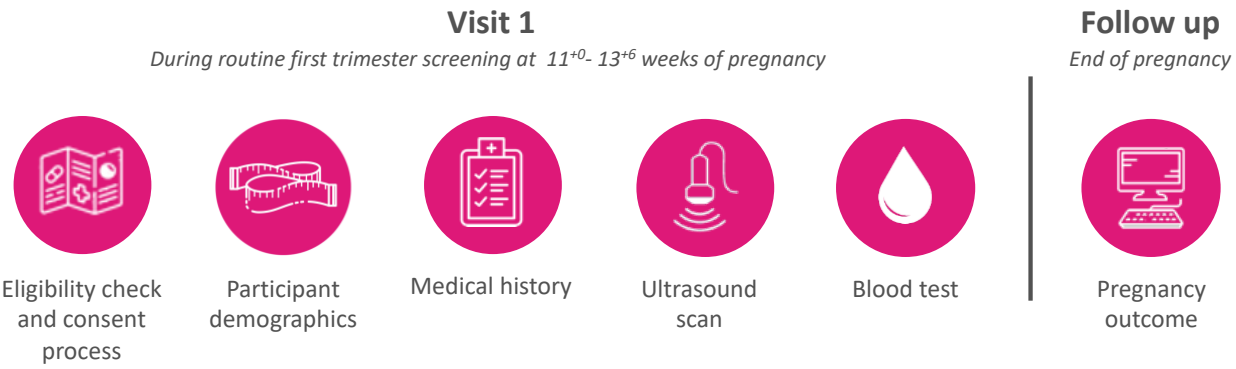
Blood test (~5min)

All participants will be asked to give up to 5ml of blood (1-2 Tablespoons). Bloods will be taken for routine testing as part of standard pregnancy care. 0.5ml of the routine blood sample will be used for research purposes to complete the Placental Growth Factor (PlGF) test and results documented in the CRF.

Follow Up

Participants will be followed up to pregnancy completion to document the outcome of each pregnancy (e.g. full term, SGA, stillbirth etc.). Pregnancy outcome will be accessed from the participant's pregnancy record which is maintained as part of routine clinical care. No physical visit or additional patient reported outcomes are required to complete follow up.

Study Flowchart



Sample Handling

Women who provide written informed consent will be agreeing that 0.5ml of the residual blood used for screening for trisomies will be used for analysis of PlGF. The laboratory is located within the Harris Birthright Research Centre and the samples will be transferred to the laboratory immediately after collection as per routine practice. Once the samples are in the lab, they will be processed after a standing time of approximately 5-10 minutes at room temperature (to allow for clotting). The tubes will be then centrifuged at 3000 rpm for 10 minutes to separate serum. 0.5ml of serum will be separated into a falcon tube and PLGF will be analysed using the Delfia Xpress (DX) machine. PerkinElmer's DELFIA® Xpress PlGF 1-2-3™ assay kit will be used for this study and results will be available in around 30 minutes.

Withdrawal Process

During the study a participant may choose to withdraw at any time. The participant does not have to provide a reason for withdrawal but if they chose to do so, this will be recorded appropriately. A participant's choice to withdraw, will have no impact on their routine clinical care.

According to the design of the study, participants may withdraw from the study in the following ways:

1. Participants may withdraw from further communication but allow the study team to continue to access their pregnancy records recorded as part of routine care.
2. Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after the date of withdrawal.
3. Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements

If a participant is deemed as ineligible as per the exclusion criteria at any point during the study, the participant will be withdrawn fully from the study. All associated data will be withdrawn, will not undergo analysis and will not contribute to the sample size.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

Definition of End of Study

The end of study is defined as 30 days post the reported pregnancy outcome of the last recruited participant to ensure all data queries have been resolved.

STATISTICS AND ANALYSIS

Statistical Analysis Plan (SAP)

To enable the analyses to be reproduced and to produce the report in a timely way, the analysis will be programmed in in the period prior to the completion of follow up. It will be documented in a stand-alone statistical analysis plan (SAP). This will include programmes, dummy tables and figures. Results will be presented according to the TRIPOD and STARD guidelines. All data and programs will be provided to an independent statistician for evaluation.

Statistical Methodology

The primary purpose of the analysis is the development and validation of multivariable predictive models for FGR. The model will be developed within the same framework used for aneuploidies, preeclampsia and FGR; using Bayes theorem to update a prior model using maternal factors with likelihoods from biomarker measurements. Each potential predictor will be assessed in terms of its ability to distinguish between those with and without FGR allowing for maternal factors. Models for likelihoods (the probability distribution of the predictor conditional on outcome and on maternal factors) will be fitted and combined with the prior model using Bayes theorem. Dependencies between predictors

conditionally on outcomes and on maternal factors will be assessed and incorporated into a multivariable prediction model. Predictive performance will be assessed in terms of sensitivity, specificity and receiver operating characteristic curve (ROC) analyses. A Bayesian approach to inference will be adopted using Markov chain Monte Carlo methods.

Sample Size

The aim of the analysis is to produce a predictive model using measurements on individuals (i.e. samples of size 1). For a useful prediction model, the degree of separation between distributions of markers between those with and those without the condition should be relatively large for example 0.5 or more standard deviations. Assuming an incidence of around 2%, a sample of 4,000 will contain around 80 cases of FGR. This is sufficient to achieve suitable power in identifying predictors and precision in model fitting. For example, a difference in means between FGR and no FGR of 0.5 standard deviations, which could be regarded as the minimum for use in prediction, would achieve significance at the two-sided 5% level with power 99%.

Procedures for Accounting for Missing Data

Multiple imputation will be used for missing data.

Procedure for Accounting for Withdrawals

If a participant is deemed as ineligible as per the exclusion criteria at any point during the study, the participant will be withdrawn fully from the study. All associated data will be withdrawn, will not undergo analysis and will not contribute to the sample size.

Decision Points

There are no planned interim analysis based on safety decision or stopping points.

DATA MANAGEMENT

Source Data

For this study, the additional 3D ultrasound images, PlGF analysed from the routine clinical blood sample, participant reported medical history will be considered source data. Data obtained regarding pregnancy outcomes and the documentation of routine clinical blood tests recorded will be taken from a participant's medical records and will be monitored as per the study specific data management and monitoring plans.

All study related documents will be stored safely in confidential conditions. On all investigation-specific documents, other than the signed consent, the participant will be referred to by their investigation specific participant number/code, not by name.

Access to Data

Direct access to study data will be granted to local research teams and authorised representatives from the Sponsor and host institution for the purposes of monitoring and/or audit of the study to ensure compliance with regulations.

Data Collection and Management

At the time of recruitment, each participant will be assigned a unique Study ID that contains no personal or identifying information about them. This will be how they are identified throughout the investigation and only the enrolment log maintained at the clinical recruiting site will contain personal and identifiable data that links the Study ID to the study participant. The enrolment log for each site will be stored securely (password protected) with restricted access to

authorised members of the clinical study team only. Investigation data collected (measurements, outcomes etc.) will be stored in a pseudonymised format using the assigned Study ID only and kept on a separate database to the enrolment log in line with GCP guidelines.

All study data will be entered on to the study specific eCRF, utilising the ViewPoint™ platform. ViewPoint™ provides exam specific reporting forms for various medical areas. Forms are composed of different sections with the required data entry fields for completion. The ViewPoint™ platform also allows the inclusion of images and graphs as well as measurements and clinical findings. All data is saved to the secure ViewPoint™ database and can be compiled into study specific reports.

Note that ICH GCP (Section 5.5) requires that electronic data entry systems are validated and that Standard Operating Procedures are maintained. ViewPoint™ is compliant with ISO 14971:2012, IEC 62304:2006, IEC 62366-1:2015 and NEMA PS 3.1-3.20. The participants will be identified by a unique number and/or code. The name and any other identifying detail will NOT be included in any data electronic file.

Only data outlined on the case report forms will be collected and entered into the electronic data capture investigation database by members of the research team. Training on how to use the investigation database shall be provided by an appropriately qualified member of the clinical research team and any subsequent training on the database will be conducted by the database supplier (GE Healthcare) in collaboration with the recruiting site as per routine practice. Any protocol specific training on data management will be conducted by the Chief Investigator, Sponsor or another appropriately delegated member of the Investigation team. In addition to using strict version control of the investigation database to prevent duplication and errors, quality checks of data entered including consistency, missing data and unusual values, shall be performed by the investigation manager and a data manager from Perspectum Ltd.

Data Handling and Record Keeping

All collected investigation data will be carefully reviewed and 'cleaned' before any final analysis and database lock is undertaken. The reason for any excluded data or data changed after database lock will be described in detail in the end of investigation report.

All paper documents containing personal data (e.g. informed consent forms) will be stored securely in a locked cabinet behind locked or ID accessed doors. Documents will be only accessible by the study's research staff and authorised personnel. The local principal investigator (PI) is responsible for keeping these documents in a secure and accessible location to ensure that, in any case of an emergency, participants can be identified and contacted readily. The enrolment log containing the linking personal data to the study ID will be kept for up to 10 years after investigation completion or until ethical approval terminates, whichever is sooner.

The investigation will comply with GDPR and relevant privacy legislation, please refer to section 12. As part of the informed consent process, participants will authorise the pseudonymous collection, use and disclosure of their investigation data by the investigators and by those persons who need that information for the purposes of the investigation, including the commercial sponsor of the investigation, Perspectum Ltd.

The pseudonymised 3D ultrasound files will be uploaded to Perspectum data transfer system called the Perspectum Portal for purposes of providing a QC to all study images. This data security infrastructure is supported by an ISO 27001, ISO 9001 and ISO 13485 compliant quality management system designed around a defence-in-depth approach with multiple layers of redundancy, surveillance, physical access controls and audit logs. Access to the Perspectum Portal is controlled and secured by Secure Sockets Layer (SSL) encryption mandating a HTTPS protocol for web-based data transmissions to prevent eavesdropping, tampering and forgery. All data are encrypted while in storage in Perspectum Portal and routinely backed-up to an alternative secondary physical location to ensure service continuity. Perspectum

Portal is hosted by Amazon Web Services (AWS), a market-leading provider of cloud platform solutions who employ rigorous and sophisticated security processes to safeguard data privacy from malicious or accidental incident. No project partner will be able to access identifiable information (except for the Local clinical research team who will upload the data).

SAFETY REPORTING

This study is an observational study with non-invasive procedures. There is one study visit associated with this study in which the 3D ultrasound images and blood biomarker, PlGF, will be collected. The only follow up will be in regard to the pregnancy outcome of each participant which can be obtained from routine medical records therefore requiring no intervention to the participant.

The 3D ultrasound and PlGF have no influence on the clinical management of participants or their routine of care. The blood sample required to measure PlGF is taken as part of routine clinical care and therefore the responsibility of the clinical recruiting site. As a result, there are no anticipated adverse or serious adverse events anticipated for this study.

INCIDENTAL FINDINGS

It is not anticipated that there will be any incidental findings as a result of this study. The additional protocols for taking the 3D ultrasound images and tests performed on the routinely collected blood sample have no clinical baring on patient management. The additional tests have not been assessed in a clinical setting therefore it would be unethical to make any clinical decisions based on these tests.

All other tests are part of routine clinical care and will be reviewed by the requesting healthcare professional.

QUALITY ASSURANCE PROCEDURES

A risk assessment was conducted prior to the study starting. Issues raised have been addressed within the final protocol and procedures have been planned to monitor the ongoing risks of the study. A risk proportionate approach will be utilised within this study and the study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Central monitoring of study procedures will be imbedded into the study management. The investigation may be monitored, or audited in accordance with the current approved protocol, monitoring plan, GCP, relevant regulations and standard operating procedures.

Direct access to the study data will be granted (where appropriate) to authorised representatives from the Sponsor, regulatory authorities, and host institution(s) for the purposes of monitoring to ensure compliance with regulations. A monitoring plan will be established for this study.

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Investigator will ensure that this investigation is conducted in accordance with the principles of the Declaration of Helsinki.

Guidelines for Good Clinical Practice

The Investigator will ensure that this investigation is conducted in full conformity with relevant regulations and with the Guidelines for Good Clinical Practice.

Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the appropriates above parties for amendments to the original approved documents.

Approval will also be sought locally by all participating sites.

Reporting

The CI shall submit, once a year throughout the investigation or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. Progress reports will also be provided to the funder at specific intervals as specified in the research contract. In addition, an End of Investigation notification and final report will be submitted to the same parties.

Participant Confidentiality

The research team will ensure that the participants' privacy is maintained. Data shall be pseudonymised such that the participants will be identified only by initials and a participant's ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by investigation staff and authorised personnel. The study will comply with the Data Protection Act 2018 and General Data Protection Regulation 2016/679.

The named investigators will have access to all pseudonymised data from the investigation. Students and collaborators may be given access to pseudonymised data under the supervision of the named investigators.

Potential risks of procedures

Ultrasound

Ultrasound is a safe and non-invasive technique with no known risks in pregnancy. The ultrasound does not involve any ionising radiation (X-rays) and all of the scans will be performed after the most sensitive period of pregnancy is completed. Furthermore, all of the 3D and Doppler scans will be of the placenta, and maternal blood vessels only. The scan will be undertaken as part of the woman's routine first-trimester ultrasound and may cause some inconvenience by adding 3-5 minutes to the routine clinical care visit.

Phlebotomy

Common risks associated with phlebotomy are pain during the procedure and bruising (with associated pain afterwards). The blood test conducted as part of this research is conducted by using residual blood from a sample taken as part of routine clinical care. No additional blood will be drawn from participants as part of this study. As a result, these risks are the responsibility of the clinical care team and will be minimised by ensuring that all staff are fully trained in phlebotomy as per local procedures. All participants will be fully informed about what is excepted from them as part of the study in the Participant Information Leaflet (PIL).

Expenses and Benefits

Where possible, all visits will take place during routine standard of care however, reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

FINANCING AND INSURANCE

Funding

This study is funded by the National Institute for Health Research (NIHR) Artificial Intelligence in Health and Care Award (AI Award). Finances and budget will be managed by the Grants team and the Clinical Project Management team under Perspectum Ltd.

The NIHR is funded through the Department of Health to improve the health of the United Kingdom through research. The views expressed are those of the researchers and not necessarily those of the NIHR or the Department of Health and Social Care.

Insurance

Perspectum Ltd. has in place a specialist insurance policy with CNA Hardy Ltd which operates in the event of a participant suffering harm as a result of their involvement in the study. NHS indemnity operates in respect of the clinical treatment that is provided.

Negligent Harm

Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the Perspectum is legally liable as the Research Sponsor will be covered by Perspectum.

Non-Negligent Harm

Indemnity and/or compensation for harm arising specifically from an accidental injury and occurring as a consequence of the Research Subjects' participation in the investigation may be covered by Perspectum.

Complaints Handling

Participants will be asked to address any of their concerns regarding aspects of the study to a member of the research team. If the complaint is regarding a member of the research team, the participant will be encouraged to contact the local site's Patient Advice Liaison Service (PALS).

If participants have any questions or complaints about how their Personal Data are being processed or about any aspect of the way in which they have been approached or treated during the course of the study, they can contact the Sponsor at clinicalresearch@perspectum-diagnostics.com. Participants will be encouraged to contact the Information Commissioner's Office (ICO) for any ongoing and unresolved concerns.

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