Study Title:	Oxford Placental UltraSound (OxPLUS) Study: an observational cohort study to assess the clinical utility of the OxNNet Toolkit for the prediction of adverse pregnancy outcomes
Short Title:	Oxford Placental UltraSound (OxPLUS) Study

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Funder:	The Sir Jules Thorn Charitable Trust

Chief Investigator Signature:	
Conflict of Interest:	The Chief Investigator is a named inventor on the OxNNET Toolkit patent, however the intellectual property resides with the University of Oxford. The Chief Investigator will not receive any payment, benefit or incentive for conducting this research.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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2. LAY SUMMARY

Every baby has an inherent growth potential, failing to reach the appropriate size is called Fetal Growth Restriction (FGR). FGR is the single most common cause of stillbirth, which devastates 8 families/day in the UK. FGR babies usually have abnormally small placentas at the time of the dating scan. We have developed

a computer algorithm, the OxNNet Toolkit, which can provide fully-automated real-time measurements of placental size from a simple 3D-ultrasound scan early in pregnancy and estimate blood flow within it. These measurements will form the basis of a much-needed screening test for FGR. If we can reliably identify women at 'high-risk' of FGR early in pregnancy, we can not only carefully monitor them with extra growth ultrasound scans later in pregnancy and deliver babies with FGR before they die but also test potential therapies, such as aspirin, which could prevent FGR from developing in the first place. This study will ask 3500 women to have an extra 3-4 minute scan of their placenta at their routine first-trimester scan to see how well this simple scan predicts the outcome of their pregnancy. The aim of this study is:-

a) to assess how well the OxNNet Toolkit can predict FGR in the hands of standard NHS sonographers when embedded into the routine NHS first trimester screening

b) to assess the potential improvement in care and cost-effectiveness to the NHS of screening for adverse pregnancy outcomes with the OxNNet Toolkit

3. SYNOPSIS

Study Title	Oxford Placental UltraSound (OxPLUS) Study : an observational cohort study to assess the clinical utility of the OxNNet Toolkit for the prediction of adverse pregnancy outcomes
Short Title	Oxford Placental UltraSound (OxPLUS) Study
Study registration	Not applicable, non-interventional study
Sponsor	University of Oxford Research Governance, Ethics & Assurance (RGEA) Boundary Brook House, Churchill Drive Headington, Oxford OX3 7GB RGEA.Sponsor@admin.ox.ac.uk
Funder	The Sir Jules Thorn Charitable Trust 24 Manchester Square London W1U 3TH info@julesthorntrust.org.uk Tel: 020 7487 5851
Study Design	Prospective, Observational, Cohort Study
Study Participants	Women 18 years of age or older who have: • A singleton pregnancy • A live fetus at 11^{+0} to 14^{+1} weeks • Pregnancies with no major defects identified during 11^{+0} to 14^{+1} week scan • Full capacity to provide informed consent • Able to understand written and/or verbal English (via translator if required)
Sample Size	3500
Planned Study Period	1st Apr 2023 – 28 Feb 2026

	Participant Involvement: From routine first-trimester ultrasound appointment (between 11^{+0} to 14^{+1} weeks of pregnancy) to pregnancy completion.		
Planned Recruitment period	18 months		
	Objectives	**Outcome Measures**	**Timepoint(s)**
Primary	• To assess the ability of first-trimester OxNNet generated placental metrics (placental volume in ml and vascularity as measured with sv3-DFMBV), alone and in combination with the other risk factors included in the Fetal Medicine Foundation (FMF) fetal growth restriction (FGR) algorithm, to predict FGR.	• Fetal Growth Restriction	End of pregnancy
Secondary	• To assess the ability of first-trimester OxNNet generated placental metrics (placental volume in ml and vascularity as measured with sv3-DFMBV) to predict pre-eclampsia • To assess the ability of first-trimester OxNNet generated placental metrics (placental volume in ml and vascularity as measured with sv3-DFMBV) to predict other adverse pregnancy outcomes • To assess the performance of sv3-DFMBV in prediction of adverse pregnancy 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	End of Pregnancy
		• Neonatal death	End of Pregnancy + 28 days
		• Neonatal morbidity	End of pregnancy to discharge from the Neonatal intensive care unit

	• To assess the economic costs and benefits to the NHS should the test be added to the routine first trimester screening	• Cost-effectiveness expressed in terms of incremental cost per adverse perinatal outcome avoided	• End of perinatal period
Investigation Procedures	• First trimester 3D Ultrasound scan • Placental Growth Factor (PIGF) blood biomarker		

4. ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
EPR	Electronic Patient Records
GCP	Good Clinical Practice
GP	General Practitioner
FGR	Fetal Growth Restriction
FMF	Fetal Medicine Foundation
HELLP	Haemolysis, Elevated Liver enzymes and Low Platelets (syndrome)
HRA	Health Research Authority
ICF	Informed Consent Form
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
IVH	Intraventricular Haemorrhage
NCPAP	Nasal Continuous Positive Airway Pressure
NHS	National Health Service
NHS-FASP	National Health Service Fetal Anomaly Screening Programme
NHSLTP	National Health Service Long Term Plan
RES	Research Ethics Service
PAPP-A	Pregnancy-Associated Plasma Protein A
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PIGF	Placental Growth Factor
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture

RGEA	Research, Governance, Ethics and Assurance
SGA	Small for Gestational Age
SOP	Standard Operating Procedure
sv3-DFMBV	Single Vessel three-dimensional Fractional Moving Blood Volume
UtAD	Uterine Artery Doppler
UtADPI	Uterine Artery Doppler Pulsatility Index

5. BACKGROUND AND RATIONALE

5.1. 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).

5.2. 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 supposedly '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.

5.3. The Proposed Solution

Using deep learning (a form of artificial intelligence) 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 piece of software can automatically identify, and successfully segment, the placenta within a 3D-US image, and then estimate:

1. placental morphology (volume, 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. This piece of software can be installed on a PC and it will analyse the uploaded ultrasound scans and output numerical values for the estimated placental volume and vascularity (perfusion of that placenta).

We propose to add the OxNNet Toolkit derived placental metrics to other known risk factors to test whether this improves the predictive performance of the existing algorithms for FGR and pre-eclampsia. This should provide the much needed first-trimester, population-based screening test for risk of FGR.

5.4. 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).

5.5. 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 placental vascularity and 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, consequently the trial was not adequately powered to examine secondary outcomes such as FGR.

Our pilot data demonstrates that measuring the vascularity at 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 much needed 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).

5.6. Potential cost savings to the NHS

If clinical efficacy of the placental metrics to predict adverse pregnancy outcomes 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). This study will be fully embedded into a normal NHS ultrasound department and include a formal health economic evaluation (see Section 11.6) to assess any potential cost savings to be realised from reducing the number of unnecessary ultrasound scans and antenatal appointments, as well as the cost-effectiveness of routine employment of the screening test.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To assess the ability of first-trimester OxNNet generated placental metrics (placental volume in ml and vascularity as measured with sv3-DFMBV), alone and in combination with other risk factors included in the FMF FGR algorithm , to predict FGR.	Fetal Growth restriction (FGR) defined according to the ISUOG Delphi consensus guidelines for diagnosis of FGR (21)	End of pregnancy
Secondary Objectives To assess the ability of first-		

trimester OxNNet generated placental metrics (placental volume in ml and vascularity as measured with sv3-DFMBV), alone and in combination with other risk factors included in the FMF FGR algorithm, to predict the following outcomes:-		
• Small for Gestational Age (SGA)	• <10 centile on population-based centiles • <10th centile on customised centiles	End of Pregnancy
• 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)	End of Pregnancy
• 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)	End of Pregnancy
• 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)	End of Pregnancy
• Eclampsia	• Defined by the ACOG guidelines for hypertensive disorders of pregnancy (22) - Pre-term eclampsia (delivery <37 weeks) - Late onset eclampsia (delivery ≥37 weeks)	End of Pregnancy
• 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	End of Pregnancy
• Preterm birth	• Birth ≥24^{+0} weeks <37^{+0} weeks	End of Pregnancy
• Miscarriage	• Live fetus at the first-trimester ultrasound scan but subsequent *in utero* fetal death or delivery <24^{+0} weeks	End of Pregnancy
• Stillbirth	• Baby born with no signs of life at ≥24^{+0} weeks' gestation	End of Pregnancy
• Neonatal death	• Baby born alive but dies within the first 28 days of life	End of Pregnancy + 28 days
• 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	End of pregnancy to discharge from the Neonatal intensive care unit
To assess the cost-effectiveness of incorporating the OxNNET Toolkit into routine first-trimester scanning	Cost-effectiveness expressed in terms of incremental cost per adverse perinatal outcome avoided	End of perinatal period

7. STUDY DESIGN

OxPLUS is a prospective, observational, cohort study, which will recruit 3500 women who attend for their first-trimester pregnancy scan at a single centre, the John Radcliffe Hospital Women's Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

Participant involvement is through a single study visit involving the collection of an additional research ultrasound 3D volume of their placenta, 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) which can be taken from residual blood left over from the routinely collected sample.

The research scan will occur at the end of the routine ultrasound scan and will take an additional 3-4 minutes on top of the routine clinic visit. Placental Growth Factor (PlGF) will be measured from residual blood taken as part of routine clinical care. No additional blood samples will be required as part of this study. Patient demographics and routine medical history will be collected from the patient electronic record (EPR). All participants will be followed up until their pregnancy is completed and the outcome will be recorded from the EPR.

Women attending their first-trimester combined test screening at site (11^{+0} to 14^{+1} weeks of pregnancy) who are interested in taking part in the study will initially be screened against the inclusion criteria and those confirmed as eligible* will be invited to take part and if willing, informed consent obtained. Consented participants will then complete their only visit where the following study activities will take place:

Visit	Time	Study Activities
Visit 1	During routine first-trimester ultrasound appointment 11^{+0} to 14^{+1} weeks of pregnancy	• Eligibility check • Obtain consent • Brief medical history • Receive additional 3D ultrasound scan • PIGF measurement • Measure blood pressure, carbon monoxide reading, height & weight

** Participants may be subsequently excluded if later testing (including the 11^{+0} to 14^{+1} week scan) demonstrates any of the exclusion criteria (which will not be known at the point of consent).*

Participants will continue in the study until either the end of their pregnancy or the baby is discharged from the neonatal intensive care unit but no further in person study visits will be required with the outcome of pregnancy collected from the hospital EPR.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Women, aged 18 years or older, who are shown to have a single viable pregnancy at their first-trimester scan (11^{+0} to 14^{+1} weeks of pregnancy) and who wish to have the routinely offered NHS combined test screening for aneuploidy.

8.2. Inclusion Criteria

- Pregnant
- 18 years of age, or older
- Presenting for first-trimester combined test screening between 11^{+0} and 14^{+1} weeks of pregnancy
- Participant is willing and able to give informed consent for participation in the study.
- Able to understand written or verbal English and able to access methods of translation.
- In the opinion of the research team, the participant is not at risk or under stress or limited in their ability to participate in the study activities.

8.3. Exclusion Criteria

The participant will be excluded from the study if ANY of the following apply:

- Participant has a multiple pregnancy (more than one viable fetus) discovered at the scan
- Participant has a non-viable pregnancy discovered at the scan (no detectable heartbeat)
- Pregnancies with major defects identified during 11^{+0} to 14^{+1} week scan
- Inability for whatever reason to complete the combined test (e.g. unable to obtain nuchal translucency measurement or lack of availability of PAPP-A blood result)
- Any pregnancy subsequently found to be chromosomally abnormal as a result of either prenatal or postnatal testing

9. PROTOCOL PROCEDURES

9.1. Recruitment

OxPLUS is a single centre study, recruiting participants at the Women's Centre, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. The centre provides ultrasound scanning for all the women booked at the John Radcliffe Hospital for their pregnancy care.

In accordance with standard practice, all expectant mothers who receive their maternity clinical care in the Thames Valley receive a routine letter with information about their first scan ('dating scan') at 10-

14 weeks gestation. The letter explains that as the hospital is an active research site, women may be approached about research currently being undertaken, and which may be relevent to them. On this basis, all women invited to attend the Women's Centre for their first-trimester screening scan will be contacted by email approximately one week before the date of their routine appointment by a member of the clinical team and sent the Patient Information Sheet (PIS) and one page summary. This ensures that potential participants are given additional time to consider their participation in the study before they attend their routine first-trimester screening appointment. Those women who are interested in participating will be able to contact the research team via telephone or email ahead of their appointment to ask questions or discuss any concerns. Women may also contact the research team to advise that they are not interested, in which case they will not be approached again during their routine appointment.

Posters advertising the study will also be made available to community midwives within the Oxford University Hospitals NHS Foundation Trust area to be placed in GP surgeries and clinics where community midwives conduct antenatal appointments. Patients who are interested in participating will be able to scan a QR code to take them to the study website to find out more information about the study or contact the local research team directly via telephone or email.

Those women who, prior to their routine appointment have not already declined participation, will be approached on the day of their appointment by a member of the local research team and offered the PIS, consent form and one page summary to read. All participants will be given the time to consider the study and will have an opportunity to discuss their involvement with a member of the research team prior to the informed consent process.

9.2. Screening and Eligibility Assessment

Women attending their first-trimester scan at site (11^{+0} to 14^{+1} weeks of pregnancy) who are interested in taking part in the study will initially be screened against the inclusion criteria and those confirmed as eligible will be invited to provide informed consent. At this stage the eligibility of participants can only be assessed against the inclusion criteria since the exclusion criteria cannot be fully assessed until after the routine first-trimester scan has been completed. No study specific procedures (e.g. 3D ultrasound scan or measurement of blood pressure) will be completed or any other study data collected until the routine ultrasound scan demonstrates that the participant does not meet the exclusion criteria.

Participants will be accepted into the study on the basis of this initial eligibility screening and their willingness to provide consent. However, it is anticipated that a percentage of participants will be lost once the routine clinical fetal ultrasound scan has been completed where one or more of the exclusion criteria have been identified (such participants will be deemed ineligible, no further study assessments or data collection will take place and they will be fully withdrawn from the study. See section 9.10).

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information Sheet and Informed Consent will be presented to the participants detailing: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, with the opportunity to ask any questions and confirm their full understanding of the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. This will routinely be captured electronically directly onto a form held on the data capture tool (see Section 12.3) and collected via a tablet device handed to the participant during the informed consent discussion. Paper copies of consent forms will also be available in the event that the data capture tool is unavailable due to technical or other issues. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be provided to the participant via secure email directly from the tablet device or in the absence of an email address can be printed and handed to the participant. In the case of a paper consent form being signed, a paper copy will be provided. The original signed form will be retained at the study site.

9.4. Enrolment

Consented participants will be confirmed as enrolled participants once it is clear that none of the exclusion criteria have been identified at the routine first-trimester scan. This is an observational study only and no randomisation will be necessary.

9.5. Blinding and code-breaking

This is an observational study. No blinding will be required.

9.6. Description of the OxNNET Toolkit

The OxNNet toolkit is a unique piece of software that can be installed on a PC. It will automatically analyse an uploaded ultrasound scan and output numerical values for the estimated placental volume and vascularity (perfusion of that placenta). These ultrasound biomarkers are known to predict adverse pregnancy outcomes e.g. a small placenta with normal perfusion means the pregnancy is at risk of FGR whilst a small but hypoperfused placenta has a risk of developing pre-eclampsia (17).

9.7. Study Visit

Participants will be required to attend a single study visit, which will take place at the same time as their routine 11^{+0}-14^{+1} week first trimester scan. Routinely, women who attend this visit will be offered a choice of either a pregnancy dating scan in which case an ultrasound scan will be the only test or a woman may choose to have the combined screening test which also requires a blood sample to be taken to analyse for genetic abnormalities (aneuploidy). Only women who elect to have the combined screening test with the

additional blood test will eligible for the study. For women who have consented to participate in the study, the following activities will take place during the study visit:

Activities	Study Visit
Eligibility check	X
Informed consent	X
Brief medical history	X
Basic measurements (BP, height & weight, carbon monoxide reading)	X
3D Ultrasound scan	X
Placental Growth Factor (PlGF) blood biomarker	X

Brief Medical History:

The local research team will obtain basic information about the participant's medical history in particular any history of hypertension, both outside and during pregnancy, or diabetes.

Basic Measurements:

The local research team will record the BP of participants in both arms, a carbon monoxide reading and their height and weight.

Demographics & Medical History:

All further medical history data including any medication that they are currently taking and details of their pregnancy will be taken from the participant's EPR. Any additional demographic data (e.g. ethnicity), as collected routinely, will also be obtained either as reported by the participant or from the EPR.

3D Ultrasound Scan:

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

All participants give up to 5ml of blood for routine testing of two biomarkers for aneuploidy as part of the the combined test, offered as standard pregnancy care. 0.5ml of residual blood from the routine blood sample will be used for research purposes to complete the Placental Growth Factor (PlGF) test. PIGF has been identified as an independent biomarker for FGR and the result will be added to the multifactorial algorithm which the study will use to predict FGR.

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.

9.8. Subsequent Visits

Not applicable.

9.9. Sample Handling

Approximately 5 ml of blood (1-2 teaspoons) will be collected from participants for routine testing as part of standard pregnancy care to be used for screening for trisomies 21, 18 and 13. 0.5ml of the residual blood will be used for the study-specific analysis of PlGF. This additional analysis for PIGF will be performed alongside the routine analyses by the Clinical Biochemistry laboratory located within the John Radcliffe Hospital, Oxford. 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 PIGF 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. All study specific blood samples will be destroyed according to local NHS laboratory procedure once analysed.

Results of the PIGF analysis will be made available to the research team using the participants study ID as an output from the Perkin Elmer 'Life Cycle' software.

9.10. Early Discontinuation/Withdrawal of Participants

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 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.

2. 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.

9.11. Definition of End of Study

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

10. 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 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.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here. A full statistical analysis plan will be finalised before any analysis takes place.

11.2. Description of the Statistical Methods

The first trimester 3D-US placental volume and the vascularity features will be assessed using logistic regression (allowing for non-linear relationships) to determine if they are predictive of FGR and/or other adverse outcomes including pre-eclampsia. Note that these univariable analyses will be for descriptive purposes only, and will not affect the choice of variables entering the multivariable model. Bivariate correlations will be examined to detect multicollinearity (inter-dependence of the variables) within the novel variables and with the known risk factors (maternal smoking status, serum PAPP-A etc.). Any independent OxNNet metrics which are non-collinear will be included in a multivariable logistic regression model, using appropriate variable selection techniques, to explore if there is any improvement in predictive ability by combining those variables into a multivariable model. The modelling process will explore non-linear relationships for continuous variables, and may include pre-defined interaction terms. Internal validation will be carried out using bootstrapping to account for the optimism of the model-development. The predictive ability of the variables individually, and any generated multivariable model, will be determined using standard performance assessment metrics (i.e., discrimination, calibration, and net-benefit). Missing data (for covariates and outcomes) is expected to be low, however if there is a significant amount (>5%) then we may use multiple imputation techniques.

11.3. Sample Size Determination

Based on recent recommendations (28) and making conservative assumptions (including a C-Index of 0.9), 3019 cases would be required to develop a multivariable model for pre-eclampsia (event rate 2%) including up to 20 parameters. For FGR (event rate 5%) we would be able to include up to 50 parameters with a sample size of 3265. Therefore, we intend to collect 3500 cases to allow for potential drop-out, or slightly lower event rates.

11.4. Decision points

Interim statistical analysis will be undertaken after half of the participants have been recruited in order to assess key outcome event rates, and levels of missing data.

11.5. The Level of Statistical Significance

A 5% level of statistical significance will be used, where appropriate.

11.6. Health Economics Analysis

A health economic evaluation will be undertaken as part of the OxPLUS Study that will assess the cost-effectiveness from targeting vital NHS resources (e.g. serial growth scans) to the women who will most benefit from them. We will construct a decision-analytical model with the view to estimating alternative first trimester screening strategies for managing fetal growth restriction, including a strategy of incorporating the OxNNET Toolkit into routine first-trimester scanning and a strategy that excludes the OxNNET Toolkit.

For the alternative management strategies, cost-effectiveness will initially be expressed in terms of incremental cost per adverse perinatal outcome avoided. A decision-analytic framework provides a rigorous methodology for synthesising information from a variety of sources, including direct observations from within the OxPLUS Study. Accepted guidelines for good practice in decision-analytic modelling and the general principles outlined in the NICE 'reference case' will be followed (23, 24). The costs of performing 3D ultrasound scanning will encompass the cost of training, software, staff time required to conduct the scanning and interpret outputs, and follow-on-management, and will be estimated using primary research methods.

For all 3500 participants recruited from the unselected population, a comprehensive profile of their and their baby's hospital resource use between the routine NHS first-trimester ultrasound scan (11^{+0} to 14^{+1} weeks' gestation) and hospital discharge post-delivery will be extracted from hospital electronic patient records. This will encompass numbers of growth ultrasound scans, model of antenatal care assigned to, and duration and intensity of antenatal, intrapartum, postnatal and neonatal care, based on standard criteria for level of care, as well as maternal and neonatal surgical procedures and complications.

In addition, targeted economic studies will be integrated into the OxPLUS Study to generate key resource use and economic cost parameter estimates for the decision-analytical model. Unit costs for each resource input will be derived from national secondary sources, for example the Department of Health's National Schedule of Reference Costs, but supplemented where necessary using primary research methods.

The model will consider the clinical pathways of pregnant women from an unselected population presenting for routine first-trimester scanning, the important natural history and clinical- and event-related activity for these women, the appropriate model type (e.g. Markov or discrete-event simulation

approach) and the appropriate analytical framework (e.g. cohort analysis versus individual-level simulation). Furthermore, the decision-analytic model will provide a framework for integrating data from external studies.

A key methodological challenge will involve generating expressions of cost-effectiveness amenable to broader cost-effectiveness comparisons by decision makers. Translating the potential benefits of the OxNNET Toolkit in terms of timely prediction of fetal growth restriction and other adverse pregnancy outcomes into quality-adjusted life year (QALY) metrics is constrained by the paucity of validated utility measures in the perinatal and early childhood contexts. The utility values placed on health states within the model will be informed by our recent research in this area (25), and supplemented where necessary by primary research. Further, we will identify risk thresholds for fetal growth restriction beyond which it would be cost-effective to intervene on the basis of the results of the OxNNET Toolkit with serious growth ultrasound scans and further intervention.

Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis (26). Cost-effectiveness acceptability curves will be used to show the probability of cost-effectiveness of each of the evaluated strategies at alternative cost-effectiveness thresholds held by decision-makers (27). All costs occurring beyond the first year after birth will be discounted using nationally recommended discount rates (24).

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data).

In this study, the additional 3D ultrasound images, PlGF analysed from the routine clinical blood sample, any medical history data collected from the participant and BP readings, height and weight taken at Visit 1 will be considered as source data. Data obtained regarding additional medical history, current medications, pregnancy outcomes and the documentation of routine clinical blood tests will be taken from a participant's medical records in which case these will be considered the source data.

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

12.2. Access to Data

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

12.3. Data Recording and Record Keeping

At the time of consent, 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 study 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 will be stored securely (password protected) with restricted access to authorised members of the local study team only.

All study data will be entered on to the study specific eCRF, utilising the REDCap™ electronic data capture tool hosted at the University of Oxford. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies.

Only data outlined on the case report forms will be collected and entered into the electronic data capture database by members of the research team. Training on how to use the database shall be provided by an appropriately qualified member of the clinical research team. Any protocol-specific training on data management will be conducted by the Chief Investigator or other appropriately delegated member of the research team. In addition to using strict version control of the study database to prevent duplication and errors, quality checks of data entered including consistency, missing data and unusual values, shall be performed by members of the research team as outlined in the monitoring plan.

The 3D ultrasound images will be downloaded from the ultrasound machines at the end of each working day on to a password protected hard drive by a member of the research team. Images will then be uploaded to a password protected file on a secure University server and also a back-up device which will be stored securely in a locked cupboard within a locked office within a University department. All study-related images will be identified by Study ID only and participants will not be identifiable by the biomedical engineers who will be responsible for analysing the images.

Study data collected (measurements, outcomes etc.) and 3D ultrasound images will be stored in a pseudonymised format using the assigned Study ID only and kept on a separate database(s) to the enrolment log in line with GCP guidelines. Electronic consent forms collected via REDCap will be stored securely in a pdf archive location within the REDCap system as a read-only pdf document and accessible only by members of the research team given specific user rights to access this location. Access to this location will be limited.

Data collected on REDCap prior to the participant being deemed as eligible following the routine ultrasound scan will be limited to the e-consent form. Only once the study team are certain that the participant has not met any of the exclusion criteria, will the study team go on to collect and record other study data. E-consent forms for those participants deemed as ineligible will be stored in the REDCap system as described above.

All study 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 at the end of study report.

Any 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, all essential paper and electronic documentation, collected study data and ultrasound images will be kept for 5 years after the completion of study-related activities. Ultrasound and pregnancy outcome data identified by study ID will only be used for secondary analysis once the study file is destroyed after 5 years as this will render the data fully anonymised.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

As a non-CTIMP, observational study GCP monitoring will not be required for this study. However central monitoring of study procedures will be embedded into the study management and documented in the study specific monitoring plan to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.2. Study Committees

This is an observational study and there is therefore no requirement for an oversight committee.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA and host institutions for written approval.

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

16.4. Other Ethical Considerations

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 bearing 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.

A decision to not perform the additional 3D ultrasound scan or request the extra PIGF blood test will be made by the sonographer and/or research midwife automatically in the event of the participant having to be withdrawn due to an exclusion criterion being identified at the routine scan. This will be done discreetly without causing further distress or anxiety to the participant. In the event that an anomaly is discovered on the routine scan, there is a robust NHS process in place to support the women through the next steps and this will be managed by trained NHS staff according to routine procedures.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

The study details will be available on HRA Research Summaries.

16.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study ID only on all study documents and any electronic database(s). All documents will be stored securely and only accessible

by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

All study activities will take place during the routine standard of care first-trimester scanning appointment No expenses will therefore be paid.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the Sir Jules Thorn Charitable Trust through the Translational Biomedical Research Award. Finances and budget will be managed by the grants team and the clinical project management team within the University of Oxford, Nuffield Department of Women's and Reproductive Health.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by The Sir Jules Thorn Charitable Trust. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

Once all study-related activity has ceased, all study documentation including essential documents, source documentation and CRFs will be archived. All study documentation will be retained for 5 years after the

completion of study-related activities in accordance with the requirements of the University of Oxford. Where source data is contained within patient medical notes, archiving should be in accordance with requirements of the Oxford University Hospitals NHS Foundation Trust. Hard copy documentation will be archived offsite at a secure location by an external archiving service according to the departmental SOP on Archiving of Clinical Study Documentation. All electronic data including study documentation and any databases holding study information will be backed up onto a secure server with access restricted to authorised personnel only with a second copy transferred to a back-up media device, password protected with AES-256 encryption and stored in a locked cupboard within a locked room within the University department (access-controlled).

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22. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	29 Aug 2023	D Hedgecott/S Mathewlynn	Inclusion criteria amended to include pregnancies up to and including a crown-rump length of 84.0mm (which corresponds to a gestational age of 14^{+1} weeks) in line with current NHS-FASP guidance for the applicability of first-trimester combined screening test.
2	3.0	04 Jan 2024	D Hedgecott/S Mathewlynn	Add an additional exclusion criterion to correct an inconsistency between the protocol and study procedures.
3	4.0	04 Dec 2024	D Hedgecott	1. Extended the planned study period by five months to end 28 Feb 2026. 2.Updated the contact details to reflect a change in the lead biomedical engineer working on the study.