Non-CTIMP Study Protocol

I-TEST-M: Modelling Retina-Placental Interactions in Pregnancy

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure
PIGF	Placental Growth Factor
PAPP-A	Pregnancy Associated Plasma Protein-A
ECG	Electrocardiography
QMRI	Queen's Medical Research Institute

1 INTRODUCTION

1.1 BACKGROUND

Vascular dysfunction in pregnancy, manifesting as pre-eclampsia, fetal growth restriction, and stillbirth, causes significant morbidity and mortality worldwide for mothers and babies. Pre-eclampsia affects up to 6% of pregnancies and causes 500,00 fetal and 70,000 maternal deaths each year(1). Beyond the immediate impacts, mothers who suffer from pre-eclampsia, and children who were growth restricted in utero, have elevated risks of cardiovascular and metabolic disease throughout their lives(2,3).

National guidelines recommend aspirin prophylaxis commenced prior to 16 weeks' gestation to reduce the risk of pre-eclampsia, fetal growth restriction and stillbirth in women at high risk of placental dysfunction(4). The most effective first trimester risk prediction algorithms incorporate uterine artery Doppler measurements and blood biomarkers like placental growth factor (PlGF) or pregnancy associated plasma protein-A (PAPP-A) assessed at 12 weeks' gestation. Despite an ~82% sensitivity for preterm pre-eclampsia, this screening test is a poor predictor for pre-eclampsia occurring at >37 weeks' gestation, which is the majority of disease(5). Moreover, risk stratification tools based on one-off measurements at a single time point cannot predict likely clinical trajectory of disease or time to deterioration. The lack of robust strategies to guide management presents challenges for clinicians, in implementing appropriate prophylaxis, monitoring and timely delivery, and in minimising harms associated with excessive intervention and iatrogenic birth at unduly early gestations.

Ophthalmic artery Doppler indices show promise as predictive markers for pre-eclampsia, at both early and late gestations(6). Meanwhile, retinal microvascular changes are reported preconception, antenatally, and postpartum in women with pregnancies affected by placental dysfunction(7,8,9,10,11). The eye may therefore represent a "window" into maternal cardiovascular adaptation to pregnancy. Serial retinal vascular imaging of pregnant women longitudinally throughout gestation is being carried out through the *I-TEST* study (REC 332944), with the aim of identifying novel retinal imaging-derived biomarkers as non-invasive measures of maternal vascular responses to pregnancy.

Computational fluid dynamics and machine learning advances are enabling increasingly precise modelling of complex biological systems, including the pregnant maternal circulation. Such models can be personalised with data from pregnant individuals to produce accurate predictions of blood flows and resistances within specific vascular beds, including placental and retinal microcirculations, at greater resolutions than measurable with non-invasive techniques(12,13).

This study will be nested within the *I-TEST* study, which is recruiting patients for retinal vascular imaging at 12 and 36, or 20 and 36 weeks' gestation (cohort 1), and at 36 weeks' gestation only (cohort 2). In *I-TEST-M*, we will carry out additional assessments of *I-TEST* study participants in the form of longitudinal measurements of ophthalmic and uterine artery Doppler indices and cardiovascular metrics. Integrating these measurements with a computational modelling approach will provide insights into adaptation of the wider maternal circulation to pregnancy. It will also allow us to identify novel vascular biomarkers relating to ophthalmic artery and systemic circulatory metrics which can indicate maladaptive maternal vascular responses, and be integrated into models that are predictive of the risk of placental dysfunction.

1.2 RATIONALE FOR STUDY

Our main aim is to identify and test novel biomarkers relating to retinal vascular, ophthalmic artery and systemic circulatory blood flows, for early detection of pregnancy complications and integration into models that are predictive of pre-eclampsia, fetal growth restriction and stillbirth. We will use a computational modelling approach to simulate blood flows within the maternal circulation and investigate the relationship between changes in the retinal and uteroplacental circulations during normal pregnancies and those affected by vascular dysfunction. This approach will complement that

of the *I-TEST* study, which aims to develop retinal imaging-derived biomarkers of placental dysfunction and within which our sub-study is nested, by relating structural retinal vascular changes with physiological adaptation of the entire maternal circulation.

We hypothesise that retinal vascular changes reflect the dynamic remodelling of maternal systemic and uteroplacental circulations during pregnancy. This could provide opportunities to monitor vascular responses to pregnancy non-invasively and in real time, allowing improved risk stratification and early detection of pregnancy complications.

To test this hypothesis and achieve our study aims, we will address the following research questions:

1. How do retinal blood flows change throughout gestation during uncomplicated and disordered pregnancies, and how do these changes relate to adaptation with maternal systemic and uteroplacental circulations?
2. Do resistance patterns within the retinal microcirculation correlate with quantitative metrics derived from retinal vascular imaging?
3. Do retinal blood flows correlate with established markers of placental function and clinical pregnancy outcomes?
4. Can integrating metrics relating to retinal vascular, ophthalmic artery or systemic circulatory blood flows into predictive models of pre-eclampsia and fetal growth restriction improve their performance, over and above current clinical tools?

We anticipate that biomarkers derived from computational models of the maternal cardiovascular system, as it evolves dynamically throughout gestation, will have utility for serial assessment of pregnant women to monitor their vascular adaptation to pregnancy. This could enable clinicians to manage pregnancies where vascular dysfunction is suspected with a more nuanced, personalised and timepoint-specific approach.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To collect a range of non-invasive cardiovascular and ultrasound Doppler blood flow metrics longitudinally throughout pregnancy, from women enrolled in the *I-TEST* study.

2.1.2 Secondary Objectives

To integrate the cardiovascular and ultrasound Doppler measurements into personalised computational cardiovascular models that capture changes in vascular resistances and compliances, including within retinal and uteroplacental circulations.

To collect serial urine samples for assessment of proteinuria levels (in addition to blood samples at 36 weeks for measurement of biomarkers of placental dysfunction, and data on key maternal and neonatal outcomes, collected as part of the *I-TEST* study). This will allow correlation of maternal cardiovascular changes with markers of renal microvascular dysfunction, established predictive biomarkers for placental dysfunction, and clinically relevant metrics.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Generation of circulatory models which simulate blood flows and vascular resistances throughout the maternal circulation at serial timepoints throughout gestation.

2.2.2 Secondary Endpoints

Identification of vascular biomarkers from computational models which can discriminate pregnancies affected by placental dysfunction from healthy pregnancies.

Correlation of retinal and ophthalmic artery haemodynamic metrics derived from computational modelling with structural parameters derived from retinal vascular imaging (through comparison with *I-TEST* study results).

Validation of novel vascular biomarkers against established markers of vascular and placental dysfunction, and subsequent integration of vascular biomarkers into models which are predictive of clinical pregnancy outcomes.

3 STUDY DESIGN

This is an observational study, designed to characterise the maternal cardiovascular response to pregnancy for subsequent identification of vascular biomarkers of placental dysfunction which are suitable for integration into predictive models. It is nested within the *I-TEST* study, through which participants will undergo serial multimodal retinal imaging between 9 and 39 weeks' gestation.

We propose additional assessments of *I-TEST* study participants, in two sequential study arms:

a. women recruited in late pregnancy, comprising those with healthy pregnancies (controls) and those with diagnosed pre-eclampsia or fetal growth restriction (cases), studied at fortnightly intervals until birth (phase one); and

b. women studied longitudinally at approximately 12, 28 and 36 weeks' gestations, and 6 weeks postnatally (phase two). These will be an unselected pregnant cohort, enriched with those at higher risk of placental dysfunction who will be invited to additional study visits in late pregnancy to coincide with appointments for fetal monitoring as clinically indicated.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Phase one: 20 pregnant women with singleton pregnancy recruited after 34 weeks' gestation, including 10 with uncomplicated pregnancies and 10 with diagnosed pre-eclampsia (as per International Society for the Study of Hypertension in Pregnancy guidelines) or fetal growth restriction (as per Delphi criteria for small for gestational age)(14,15).

Phase two: 100 women with singleton pregnancy, recruited after antenatal booking and prior to 15 weeks' gestation.

This will be a single site study, involving only participants with pregnancies booked within NHS Lothian.

4.2 INCLUSION CRITERIA

Enrolled in *I-TEST*

Age 16-50 years

Able to give informed consent

Singleton non-anomalous viable pregnancy

Living in Lothian area

4.3 EXCLUSION CRITERIA

Women who are not pregnant

Aged under 16 or over 50 years

Women who are classified as Adults with Incapacity (AWI) as determined by midwife, GP or research team

Delivery indicated prior to 34 weeks (for phase one)

Multiple pregnancy

Diagnosed congenital anomaly

4.4 CO-ENROLMENT

We will recruit participants from those already enrolled in the *I-TEST* study. To reduce the potential burden on participants, we will aim to align *I-TEST* retinal imaging scans with *I-TEST-M* study visits.

Women will also be able to enrol in additional studies if they choose to do so.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

All participants recruited to the *I-TEST* study will be screened for eligibility by a member of the research team, and if eligible will be invited to enrol in *I-TEST-M*. Initial contact with potential participants will be by telephone call, email, or in person during attendance at routine antenatal clinics or I-TEST study visits.

5.2 CONSENTING PARTICIPANTS

All procedures will be explained to each participant either by a member of the research team, or by a video on the website, and written information will be provided on a detailed PIS. Prior to providing written consent, all participants will be given ample time to consider whether or not they would like to take part and to ask questions relating to the research. Additionally, it will be made clear both verbally and in writing that all volunteers have the right to withdraw at any time, without giving any reason, this will not affect the care they receive. Informed consent will be sought from the participant themselves as only healthy adults will be recruited. Consent may be given online – via QR code which takes to study website which then links to REDCap database where consent form is contained – or via paper on the day of the study visit.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator or research midwives. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from:

(i) all aspects of the study but continued use of data and samples collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

(ii) all aspects of the study but continued use of data and samples collected up to that point and also routine data collection at birth from the electronic health care record. To safeguard rights, the minimum personally-identifiable information possible will be collected.

(iii) all aspects of the study, including withdrawal of all data and samples collected up to the point and withdrawal from any further collection of data or samples.

Women will be able to withdraw from the study at any time by emailing or telephoning a member of the research team, whose contact details will be provided on patient facing materials, or via the website.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

All study visits will take place at the Royal Infirmary of Edinburgh. Where possible, visits will be undertaken to coincide with a routine clinical visit, or with a *I-TEST* study visit for retinal imaging.

The following datasets will be collected at study visits (in addition to data gathered through the *I-TEST* study). In phase one, these will be at fortnightly intervals (±5 days), starting after 34 weeks gestation and continuing until birth. In phase two, these will be at 12, 28 and 36 weeks' gestation and 6 weeks postnatally (±3 weeks for each timepoint), with additional (up to fortnightly) study visits offered for women with diagnosed pre-eclampsia or fetal growth restriction, if these can be aligned with scheduled clinical appointments.

Maternal physiological data:

- Maternal height and weight will be measured.

Maternal cardiovascular data:

- Heart rate and systolic and diastolic blood pressure will be measured lying, sitting and standing.
- Echocardiography or electrocardiography (ECG) cardio-impedance will be conducted for measurement of cardiac output ± aortic size.
- Pulse wave velocity: aortic central pulse wave velocity will be assessed with a tonometry-based device placed sequentially over the carotid and femoral artery in conjunction with simultaneous ECG recording. Peripheral pulse wave velocity will then be assessed with a tonometry-based device placed sequentially over either the carotid and radial arteries, or femoral and popliteal/tibial arteries, in conjunction with simultaneous ECG recording. The distance between points of pulse wave detection will be measured manually to allow calculation of central and peripheral pulse wave velocities. The measurement of pulse wave velocities, both centrally and peripherally, will be repeated three times, or until at least two measures are within 0.5m/s.

Ultrasound assessment:

- Maternal uterine artery Doppler measurements will be made and the pulsatility index from both uterine arteries will be recorded (this assessment is already carried out on all *I-TEST* participants at the 36 week visit – *I-TEST-M* would involve further repeated measurements at all study visits).
- Maternal ophthalmic artery Doppler measurements will be made, with waveforms obtained in sequence from the right eye, left eye, and again right and then left eye. The following four indices will be recorded: first peak systolic velocity, second peak systolic velocity, pulsatility index, and ratio of second to first peak systolic velocities (this assessment is already carried out on all *I-TEST* participants at the 36 week visit – *I-TEST-M* would involve further repeated measurements at all study visits).
- Maternal middle cerebral artery Doppler measurements will be made and the pulsatility index from both middle cerebral arteries will be recorded.
- For study visits after 25 weeks' gestation, umbilical artery and fetal middle cerebral artery Doppler measurements will be made and the pulsatility index of each recorded, along with the cerebroplacental ratio (calculated as the ratio of umbilical artery pulsatility index to fetal middle cerebral artery pulsatility index).

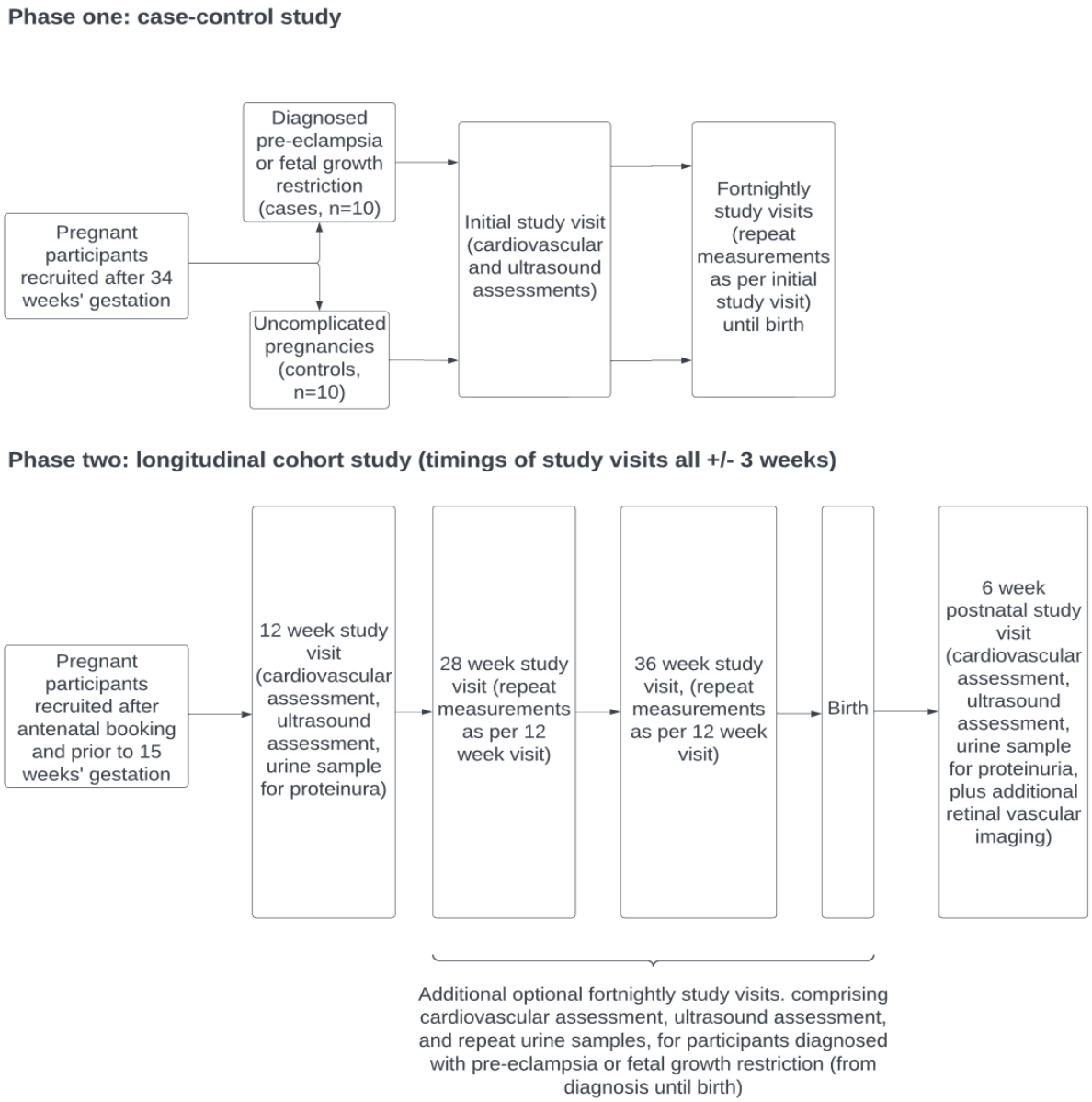
Biological samples:

- At each study visit during phase two, we will collect a urine sample for analysis of proteinuria (albumin-creatinine ratio) and for processing and storage in the Edinburgh Reproductive Tissue Biobank, allowing for future measurement of other potential biomarkers for placental or vascular dysfunction.

In addition to the serial retinal imaging carried out by I-TEST, participants recruited to phase two of I-TEST-M will undergo additional retinal imaging (scanning laser ophthalmoscopy, optical coherence tomography, and optical coherence tomography angiography) at the 6-week postnatal study visit.

Figure 1 demonstrates the schedule of visits in both phases of the study.

Figure 1: study visit schedule



6.2 LONG TERM FOLLOW UP ASSESSMENTS

There are no long term follow up assessments. We will advise participants that the overall findings of the study will be displayed on the study website. The research team will not initiate any other follow up, correspondence or study visits.

6.3 STORAGE AND ANALYSIS OF SAMPLES

Urine samples (up to 50mls) will be collected at every study visit during phase two. These will be analysed for proteinuria (albumin-creatinine level) by NHS Lothian laboratories. Excess sample will be processed and stored in the Edinburgh Reproductive Tissue Biobank within the Queen's Medical Research Institute (QMRI).

The Edinburgh Reproductive Tissue Biobank has standard operating procedures (SOPs) for processing and storage of samples. Biological samples will be retained at the end of the study in QMRI ultra-low temperature freezers, and destroyed after ten years.

7 DATA COLLECTION

A unique study identifier will be allocated to each participating woman at recruitment and this unique number will be used for data collection within the study. Identifiers are stored separately from the main data tables and only delegated members of the team will be granted access to these identifiers.

Data will be collected for all participants as part of *I-TEST* study (within which this sub-study is nested) by a delegated member of the research team using an electronic case report form (eCRF). Data collected included: a) socio-demographics, medical and obstetric history b) details of the current pregnancy including pregnancy complications. c) birth outcomes including birthweight, gestation at birth, baby sex, mode of birth, indication for delivery, admission to the neonatal unit, respiratory distress, Apgar scores and umbilical cord pH.

7.1 Source Data Documentation

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

The Investigator will maintain source documents for each patient in the study, consisting of mother and baby case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information relevant to a participant's general medical history on eCRFs must be traceable to these source documents in the patient's case notes.

7.2 Case Report Forms

Electronic case report forms will be utilised.

8 DATA MANAGEMENT

8.1 Personal Data

The following personal data will be collected as part of the research: Demographic, clinical and personal data including CHI-number; postcode; contact telephone number; email address; date of birth.

The Chief Investigator (CI) is the custodian for the study data.

8.2 Data Information Flow

Data will be extracted from the electronic health record of mother and baby and, after anonymisation, clinical details entered into the study database. Each patient will be allocated a study number that will be used to identify the patient, no personal data will be recorded in the database. Data will be filled in at each study visit.

8.3 Data Storage

Personal data will be stored by the research team on a password protected secure NHS computer in a locked office at Royal Infirmary of Edinburgh.

All local paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Access to the study documents will be by the study team only.

Research data collected will be stored on secure servers hosted by the University of Edinburgh that require user authentication.

8.4 Data Retention

Personal data will be stored for 5 years.

8.5 Disposal of Data

Research data will be archived after the end of the study, and made available in de-identified format to satisfy data sharing requirements at the end of the study.

8.6 External Transfer of Data

Data collected or generated by the study will be transferred to Swansea University for the purpose of running personalised simulations of the maternal circulations using computational models, on behalf of the Sponsors. Metrics produced from these simulations will be returned to the University of Edinburgh for further analysis by the research team.

Participants will be informed about the need for the study to share anonymised data with Swansea University for analyses.

Participants consent to the use of information about them to support other research in the future, and that the information may be shared anonymously with other researchers, whatever happens to the participant.

Data Transfer will be in accordance with General Data Protection Regulations, International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP) and SOPs that cascade from the practices defined by the Academic and Clinical Central Office for Research and Development (ACCORD) SOPs.

Delegated research staff will enter the data required by the protocol into the eCRF following training in the definitions and methods used in completing the eCRF.

On completion of data collection, the Investigator must certify that the data entered into the eCRF is complete and accurate.

Data verification and cleaning will be performed as per local procedures and detailed in the Data Management Plan.

8.7 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

8.8 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

The emphasis of phase one is integration of measured parameters into computational models of the maternal circulation. There are no comparative pregnancy cohorts, studied using haemodynamic modelling in this way, on which to base a power calculation. Given the detailed data collected at multiple time points, and additional insights afforded by a modelling approach, a sample of 10 women with uncomplicated pregnancies and 10 with disordered pregnancies will provide proof-of-principle data and indicate potential candidate biomarkers.

Regarding phases two, there are no existing pregnancy cohorts of similar phenotypic depth studied with repeated measures. Therefore, we do not have access to estimates of effect sizes to support a formal sample size calculation. After recruitment of the first 50 women, we will use initial data to calculate effect sizes and inform data collection for further recruited participants. We propose repeated longitudinal assessment of a cohort of 100 women, and aim to recruit 115 women to allow for pregnancy losses and losses to follow up.

9.2 PROPOSED ANALYSES

Participant height and detailed cardiovascular and Doppler ultrasound data collected at study visits will be used to personalise patient-specific cardiovascular models, using a two-tier parameter estimation algorithm within a closed-loop 1D-0D circulatory model of pregnancy as described in Carson et al(13). We will extract outputs from these models including predicted measures of aortic diameter and elasticity, and retinal and placental vascular bed resistances.

We will apply correlation analysis to phase one data, to assess relationships between ophthalmic artery Doppler indices and model-predicted aortic and retinal vascular metrics. This will establish whether individual Doppler indices reflect upstream or downstream vascular properties. We will also assess correlation between ophthalmic artery and uterine artery Doppler indices which might suggest synergy between retinal and uteroplacental circulations. Descriptive statistics will be used to compare measures of ophthalmic artery blood flow and retinal vascular resistances between cases and controls, identifying possible candidate biomarkers.

In phase two, we will use a linear mixed effects regression approach to assess longitudinal changes in vascular metrics within individuals, and identify differences in metric trajectories for pregnancies affected by placental dysfunction. We will validate candidate biomarkers of vascular and placental dysfunction by testing associations with proteinuria and 36-week PlGF levels (from blood samples collected as part of the *I-TEST* study), using linear models adjusted for common co-variates, adjusting for multiple comparisons. Separate subgroup analysis will be performed for participants on antihypertensive treatment.

We will assess the relationship between estimates of retinal vascular resistances generated from computational modelling and structural parameters derived from retinal vascular imaging in the *I-TEST study*, using data from phases one and two. This will be through analysis of correlation between model-prediction retinal vascular resistance and metrics derived at the same gestation from retinal imaging, for individual participants.

In predictive outcome modelling, we will adhere to PROBAST and TRIPOD guidelines(16,17). For continuous outcomes, such as birthweight, this will be approached as a multivariate linear regression task. For categorical outcomes, including occurrence of specified pregnancy complications, we will apply a logistic regression approach only for sufficiently balanced data. Training/test data splits will be performed using k-fold cross validation. We will evaluate classifiers in terms of precision, recall and area under the receiver-operator curve, and compare these with baselines based on demographic and routine clinical evaluation data.

10 ADVERSE EVENTS

All researchers involved in this study envisage that the extent of adverse events would remain low. All measurements are non-invasive and have been conducted safely in pregnancy without any adverse events. However, in the event of an adverse event, the appropriate investigator will investigate the causality, seriousness and severity. Should any woman be anxious about any of the tests or findings, our experienced team will be available for discussion. The only identified risk is in data security (Table 1).

Table 1: Main risks to data security

Risk description	Security controls	Likelihood	Impact	Risk
Unauthorised access to patient records	NHS Lothian contract of employment. Personnel mandatory training	Low	Medium	Low
Unauthorised access to NHS Lothian servers	Role based and password protected access to NHS Lothian systems with staff working on dedicated NHS Lothian equipment is secure locations	Low	High	Medium
Risk of disclosure of data leaving the NHS Lothian server	Data extracts pseudonymised, disclosure checked before release. SOPs and training according to national guidance	Low	High	Medium
Loss or unauthorised access to data during data transfer between the University of Edinburgh and Swansea University	Data release checked before release. A secure File Transfer Protocol process must be used	Low	Medium	Medium

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the Sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the Sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if a study specific risk assessment is required.

If required, a study specific risk assessment will be performed by representatives of the Sponsor(s), ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans.

If considered necessary, ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of ICH GCP.

Before the study can commence, all necessary approvals will be obtained and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Sponsor(s).

The Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs).

12.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. This is not a mandatory requirement unless deemed so by the Sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 Data Protection Training

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance Data Protection training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

12.2.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

12.2.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification, review and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to implementation and prior to participants being enrolled into the amended protocol.

13.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

13.2.1 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

13.2.2 Management of Deviations and Violations

Deviations and violations are non-compliance events discovered after the event has occurred. Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Sponsors every 3 months. Each protocol violation will be reported to the Sponsor within 3 days of becoming aware of the violation.

Deviation logs will be maintained for each site in multi-centre studies.

Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsor(s) (qa@accord.scot) must be notified within 24 hours. It is the responsibility of the Sponsor(s) to assess the impact of the breach on the scientific value of the study, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 10 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Sponsor.

13.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the Sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and Sponsor(s) within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Sponsor(s) via email to researchgovernance@ed.ac.uk.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Not applicable.

13.7 INSURANCE AND INDEMNITY

The Sponsor(s) are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Sponsor(s)' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor(s) require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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