PLANES

Placental Growth Factor Led Management of the Small for Gestational Age Fetus: A Feasibility Study.

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Protocol Approval

I, the undersigned, hereby approve this clinical study protocol.

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General Information

This document describes the PLANES study and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care has been taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the study, but centres entering patients for the first time are advised to contact the coordinating centre (Harris Research Centre) to confirm they have the most up to date version.

Clinical Queries

Clinical queries should be directed to Dr Andrew Sharp who will direct the query to the appropriate person.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, Sponsor Standard Operating Procedures.

UK Registration

This study will have Health Research Authority (HRA) Approval. All research sites will confirm capacity and capability to conduct the study and will sign a Research Site Agreement.

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This study is funded by the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) funding body as part of competition 34, with an associated study reference of PB-PG-0817-20021.

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GLOSSARY OF ABBREVIATIONS

AE	*Adverse Event*
AGA	*Appropriate for Gestational Age*
CI	*Chief Investigator*
eCRF	*Electronic Case Report Form*
CTG	*Cardiotocography*
cCTG	*Computerised Cardiotocography*
CTU	*Clinical Trials Unit*
EDD	*Estimated Delivery Date*
EDF	*End Diastolic Flow*
EFW	*Estimated Fetal Weight*
HCA	*Hierarchical Cluster Analysis*
HRA	*Health Research Authority*
GCP	*Good Clinical Practice*
FGR	*Fetal growth restriction*
IB	*Investigators Brochure*
ICH	*International Conference on Harmonisation*
ICF	*Informed Consent Form*
IOL	*Induction of Labour*
IQR	*Inter Quartile Range*
IS	*Information Security*
ISDMC	*Independent Safety and Data Monitoring Committee*
ISF	*Investigator Site File*
LCTC	*Liverpool Clinical Trials Centre*
LWH	*Liverpool Women's Hospital*
MCA	*Middle Cerebral Artery*
MRSA	*Methicillin-resistant Staphylococcus*
MTA	*Material Transfer Agreement*
NHS	*National Health Service*
NICE	*National Institute for Health and Care Excellence*
NICU	*Neonatal Intensive Care Unit*
NIHR	*National Institute for Health Research*
PCA	*Principal Components Analysis*
PI	*Principal Investigator*
PID	*Participant Identification Number*

PIS	*Participant Information Sheet*
PlGF	*Placental Growth Factor*
RCOG	*Royal College of Obstetricians and Gynaecologists*
RCT	*Randomised Controlled Trial*
REC	*National Research Ethics Committee*
RfPB	*Research for Patient Benefit*
RSA	*Research Site Agreement*
RSI	*Reference Safety Information*
SAP	*Statistical Analysis Plan*
SFH	*Symphysial Fundal Height*
s-Flt1	*Soluble fms-like tyrosine kinase-1*
SGA	*Small for Gestational Age*
SAE	*Serious Adverse Event*
SIV	*Site Initiation Visit*
SMF	*Study Management Folder*
SMG	*Study Management Group*
STV	*Short- term variability*
ToP	*Termination of Pregnancy*
TSC	*Trial Steering Committee*
TMS	*Trial Management System*
UA	*Umbilical Artery*
wGA	*Weeks' Gestational Age*
WI	*Working Instructions*
WP	*Work Package*

KEYWORDS

Fetal Growth Restriction (FGR), Small for Gestational Age (SGA), Placenta, Growth

PROTOCOL SUMMARY

This protocol describes the PLANES Study and provides information about procedures for entering participants. Every care has been taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator, Dr Andrew Sharp.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017). It will be conducted in compliance with the protocol, the EU General Data Protection Regulation (GDPR) 2016/679 and Data Protection Act (DPA) 2018, and other regulatory requirements as appropriate.

Title: PLANES: Placental Growth Factor Led Management of the Small for Gestational Age Fetus: A Feasibility Study.

Design: PLANES is a randomised controlled feasibility study of women with an ultrasound diagnosis of a fetus as being small for gestational age (SGA). Study participants will be randomised into two groups in a 3:1 ratio in favour of sFlt-1/PlGF ratio led management vs standard care. Women with an SGA fetus and a normal sFlt-1/PlGF ratio will have a repeat ultrasound and sFlt-1/PlGF ratio every 2 weeks with planned delivery delayed until 40 weeks. In those women with an SGA fetus and an abnormal sFlt-1/PlGF ratio we will offer delivery from 37 weeks, or sooner if there are other concerning features on ultrasound. Women assigned to standard care will have an sFlt-1/PlGF ratio taken but the result will be concealed from the clinical team with their pregnancy being managed as per the local NHS hospital policy.

Results from this pilot study along with health economic and qualitative elements will determine feasibility and inform the design of a future large randomised controlled trial powered for adverse pregnancy outcome. Women who prefer not to be randomised will still be offered the opportunity to participate by having an sFlt-1/PlGF ratio test but the result will not be used to guide management.

Aim: To assess the feasibility and acceptability of using the sFlt-1/PlGF ratio to refine SGA pregnancy management pathways. A mixed method approach has been adopted including a pilot trial and qualitative research with women and clinicians to address the following objectives.

Objectives:	(1) To assess the feasibility of sFlt-1/PlGF ratio led management of women with an SGA fetus (2) To assess the acceptability of such an approach to women and clinicians (3) To explore the feasibility / acceptability of the study design as an external pilot to inform the design of a subsequent randomised controlled trial (RCT)
Outcomes:	Feasibility of conducting a randomised clinical trial to investigate the effectiveness and cost-effectiveness of sFlt-1/PlGF led management of SGA fetuses
Inclusion Criteria:	Singleton pregnancy Age ≥16 years 32^{+0} – 37^{+6} weeks of gestation Estimated Fetal Weight (EFW) <10th centile on ultrasound Normal Umbilical Artery Doppler (defined as present End Diastolic Flow (EDF) and Pulsatility Index (PI) within the normal range for gestation)
Exclusion Criteria:	Unable to give informed consent Known or suspected structural / chromosomal fetal abnormality Absent or reversed End Diastolic Flow (EDF) in the Umbilical Artery (UA) on Doppler study Severe maternal disease requiring urgent delivery
Duration:	45 months, 12 months recruitment

Figure 1. PLANES Study Consort Diagram:

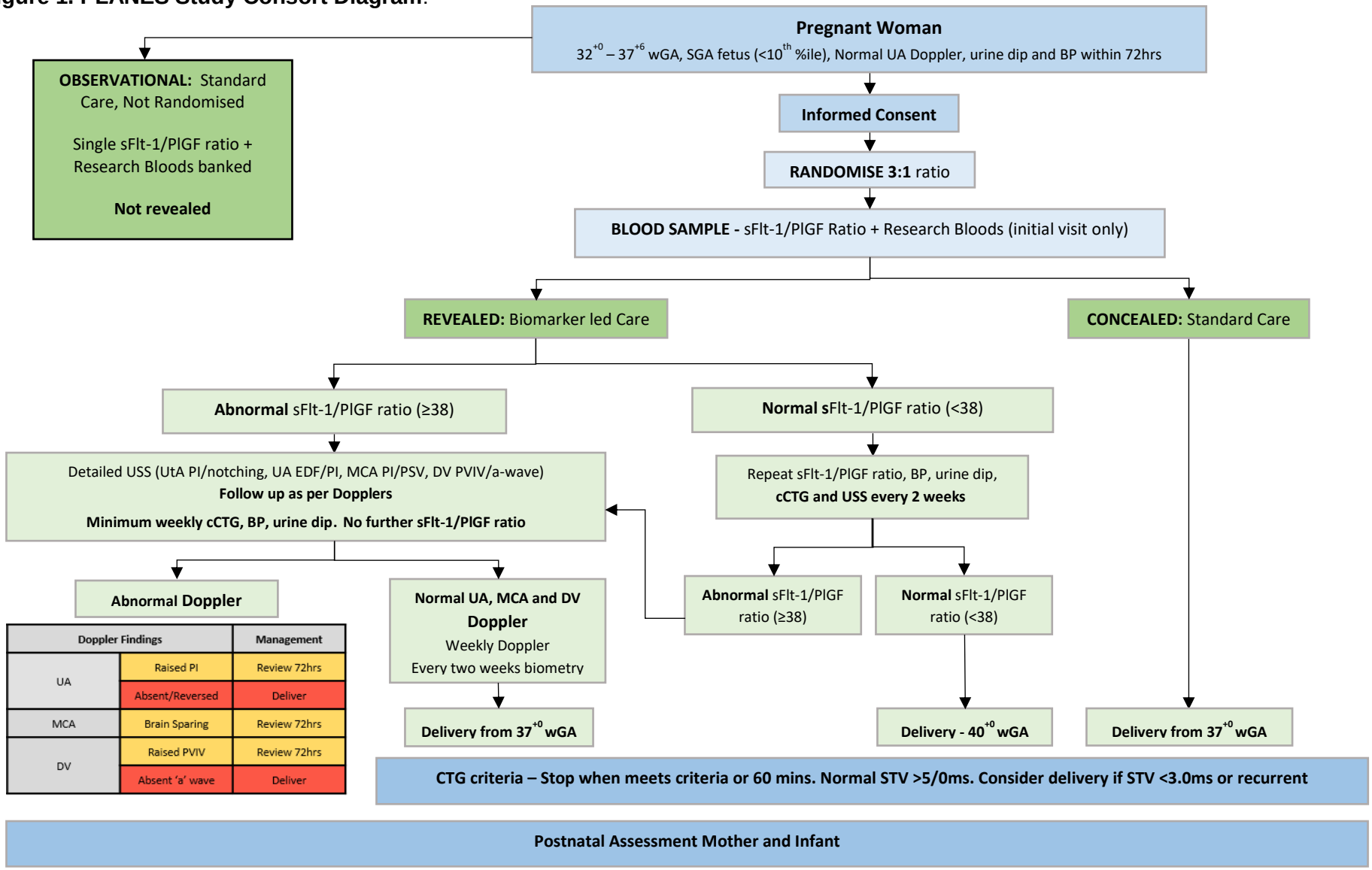


Table of Contents

1. INTRODUCTION 18

1.1 Background 18

1.2 Why is this research so important? 19

1.3 Review of existing evidence 20

1.4 Study Objectives 22

1.5 Potential Risks and Benefits 22

2. STUDY DESIGN 23

2.1 Outcome Measures 24

3. STUDY POPULATION 24

3.1 Pre-registration / Randomisation Procedures 24

3.2 Inclusion Criteria 25

3.3 Exclusion Criteria 25

3.4 Withdrawal Criteria 25

3.5 Patient Transfers 26

3.6 End of Study 26

3.7 Stopping Criteria 26

4. ENROLMENT AND RANDOMISATION 27

4.1 Participant Selection 27

4.2 Consent 28

4.3 Enrolment and Baseline 28

5. STUDY INTERVENTION 28

5.1 Detailed Study Procedure 28

5.2 Co-enrolment Guidelines 32

5.3 Concomitant Medications 32

6. ASSESSMENT AND PROCEDURES 36

6.1 Schedule of Study Procedures 32

6.2 Total Blood Volume 32

6.3 Clinical Procedures 32

6.4 Adverse Events 33

6.5 Vital Signs 33

6.6 Clinical Laboratory Assessments 33
6.7 Maternal Assessments 33
6.8 Fetal Assessments 33
6.9 Other Assessments 34
6.9.1 Special Laboratory Procedures 34
6.9.2 Shipment of Samples 35
6.9.3 Storage of Samples 35
6.10 Loss to Follow up 35
6.11 Study Closure 36
7. STATISTICAL CONSIDERATIONS 39
7.1 Introduction 39
7.2 Outcome Measures 40
7.2.1 Women, Partner and Clinician Perspectives 40
7.2.1.1 Design 40
7.2.1.2 Selection of Participants 40
7.2.1.3 Eligibility 42
7.2.1.4 Procedures 42
7.2.1.5 Mixed Methods / Qualitative Analysis 44
7.2.2 Health Economic Outcome Measures 44
7.3 Sample Size 45
7.4 Interim Analysis and Monitoring 45
7.5 Statistical Methodology 45
7.5.1 Participant Groups for Analyses 45
7.5.2 Significance Levels 45
7.5.3 Missing Data 46
7.5.4 Exposure to Intervention 46
7.5.5 Trigger for Final Analysis 46
7.5.6 Data Descriptions 46
7.5.7 Exploratory Analyses 46

8. SAFETY 46
8.1 Introduction 46

8.2 Definitions 46
8.2.1 Adverse Event 46
8.2.2 Serious Adverse Event 47
8.3 Notes on Adverse Event Inclusions and Exclusions 47
8.3.1 Include 47
8.3.2 Do not Include 48
8.4 Notes on Grading Adverse Events 49
8.5 Relationship and Study Intervention 50
8.6 Expectedness 50
8.7 Reporting 51
8.7.1 Non-Serious Adverse Events 51
8.7.2 Serious Adverse Events 51
8.7.3 Guidance on Reporting Serious Adverse Events 51
8.7.4 Additional Reporting 52
8.7.5 Safety Plan 52
9. REGULATORY ASPECTS 53
9.1 Medical Research Ethics Approval 53
9.2 Informed Consent Process 53
9.3 Study Discontinuation 54
9.4 Confidentiality 54
9.5 Quality Assurance and Quality Control of Data 54
9.6 Records Retention 54
9.7 Indemnity 55
9.8 Sponsor 56
9.9 Funding 56
9.10 Audits 56
10. STUDY MANAGEMENT / OVERSIGHT 56
10.1 Study Management Group (SMG) 56
10.2 Study Oversight Committees 57
10.2.1 Trial Steering Committee (TSC) 57
10.2.2 Independent Safety and Data Monitoring Committee (ISDMC) 58

11. MONITORING 59
11.1 Risk Assessment 59
11.2 Source Data 60
11.2.2 Source Documents 60
11.3 Data Capture Methods 60
11.3.1 Electronic Case Report Forms (eCRF) 60
11.4 Monitoring Methods 61
11.4.1 Green Light Process 61
11.4.2 Site Research Staff 62
11.4.3 Oversight 62
11.4.4 Safety Reports 62
11.4.5 Eligibility and Consent 63
11.4.6 Participant Confidentiality 63
11.4.7 Recruitment 63
11.4.8 Protocol Violations / Deviations 63
11.4.9 Withdrawals / Loses to Follow up and Missing Data 64
11.4.10 Data Management Plan 64
11.4.11 Centre for Women's Health Research Staff 64
11.4.12 Statistical Monitoring 65
11.5 Clinical Site Monitoring 65
11.5.1 Direct Access to Data 65
11.5.2 Confidentiality 65
11.5.3 Quality Assurance and Quality Control of Data 65
11.5.4 Records Retention 66
12. ARCHIVING 66
13. PUBLICATION 67
14. PROTOCOL AMENDMENTS 68
15. REFERENCES 70

List of Tables

Table 1 Stillbirths by normal and abnormal PlGF and sFlt/PlGF ratio 22
Table 2. Schedule of Study Related Procedures 37
Table 3. Grading of Adverse Events 49
Table 4. Definition of Causality / Relatedness 50

List of Figures

Figure 1. Planes Study Consort Diagram 12
Figure 2. ROC curve of stillbirth related to diagnostic test. 21
Figure 3. Participant Management Pathway 31

1. INTRODUCTION

1.1 Background

The stillbirth rate within the United Kingdom (UK) remains one of the highest in industrialised countries (3.87 per 1000 births) [1], but stillbirths remain rare at term (2.0 per 1000 births) [2]. Historically strategies to prevent stillbirth focussed on risk factors in early pregnancy [3-9]. However, risk factors alone predict less than 20% of all stillbirths [8]. Furthermore, 33% of stillbirths occur after 36^{+0} weeks, 85% prior to labour with the cause of death in 39% unknown, although 1/3 are found to be growth restricted [8]. These small for gestational age (SGA) fetuses are at a significantly higher risk of stillbirth (OR 7.01) [10-12], neonatal adverse outcome [13] and have potential life-long health risks [14, 15]. Therefore, the focus of stillbirth prevention has moved to identifying the SGA fetus.

Unfortunately, our tools to diagnose SGA are not as reliable as we would wish. The standard approach advocated for all pregnant women in the UK by The National Institute for Health and Care Excellence (NICE) relies upon serial measurement of the maternal abdomen with a tape measure from 24 weeks to generate the symphysial fundal height (SFH) [16]. SGA is suspected when the SFH measurement is <10th centile or there is static growth over two measurements. SFH measurement in isolation has a sensitivity of 30-40% [18, 19] and with no randomised controlled studies of its effectiveness [20]. Therefore, confirmatory ultrasound assessment is required, with SGA commonly defined as an estimated fetal weight (EFW) <10th centile [4, 17, 18]. However, the increase in detection of SGA with ultrasound is limited, with up to 41% of SGA fetuses remaining undiagnosed and a false positive rate of up to 20% [19].

The Royal College of Obstetricians and Gynaecologists (RCOG) has produced guidance for the management of the SGA fetus [18] but the Cochrane Collaboration acknowledge that the most appropriate regimen for surveillance is unclear [20]. This guidance advocates that the SGA fetus should have growth assessed with ultrasound every 2 weeks with additional fetal blood flow (Doppler) assessments. Timing of delivery is suggested to be based upon deterioration in fetal growth or feto-placental Doppler (<37 weeks) or when the pregnancy reaches 37^{+0} weeks even if all other factors are normal [18]. Therefore, the NHS currently has a system for the management of the SGA fetus and prevention of stillbirth based upon SFH and confirmatory ultrasound with delivery from 37+0 weeks. This 'one size fits all' approach maintains a safety margin to prevent stillbirth but leads to an increase in interventions, such as induction of labour (IOL) [21]. IOL rates for SGA are increasing (3.0% in 2012 to 10.7% in 2016 - LWH local data) with up to 40% of all pregnancies now induced (LWH local data).

Our recent survey of UK obstetric units demonstrates that this is a UK wide phenomenon with mean induction rates at 30% (range 17-46%) (Sharp et al. Accepted EJOG 2018), with 67% of responders observing an increase over 5 years and 90% stating that in their opinion SGA management had been a factor. This increased intervention and delivery of SGA fetuses at a late preterm or early term gestation, whilst well intentioned is not without concern. There is a substantial body of evidence showing that being born <39 weeks has an impact upon a child's cognitive development and later academic achievement [22-25]. Furthermore, whilst overall numbers of affected children are low, the term SGA fetus has a cerebral palsy risk 5-7 times greater than normal birth weight term babies [26, 27]. There is also an impact on women's choice as to place and mode of birth, especially when in general the risk of stillbirth is low [28] with intervention potentially not required for all SGA fetuses.

1.2 Why is this research important?

The desire to reduce stillbirth is powerful but currently leads to increased intervention for a large number of women which impacts upon women's choice and increases the burden on the health care system. However, most importantly so far it has failed to achieve its goal of significantly reducing stillbirth. We cannot ignore the association between stillbirth and SGA but likewise we do not see the current system as sustainable for patients or health care providers. Especially as not all national guidelines are as prescriptive on the management of SGA as the RCOG, recently reviewed by McCowan et al. [29]. Canadian [30] guidance suggests close monitoring of fetal condition with ultrasound after 37 weeks but with no defined time to deliver. Irish [31], United States of America and New Zealand guidance [32] is also more generous suggesting that in the presence of normal Doppler studies the SGA fetus can be left until 38-39 or 40 weeks respectively. Much of this evidence for lack of harm from delaying delivery comes from the DIGITAT study that showed no adverse effects from induction of labour vs delayed delivery [33], though this study was underpowered to offer unequivocal evidence regarding perinatal mortality or severe morbidity. Recently some reaction against early delivery for SGA in the absence of other risk factors has been observed with a recent UK study deferring delivery until 40 weeks if fetal assessment was normal [31]. However, in this study there was a single stillbirth in the deferred cohort and we feel that this demonstrates that additional reassurance of fetal wellbeing is required. We suggest a potential 'middle ground' would be to refine the risk of adverse pregnancy outcome in SGA pregnancies with biomarkers of placental function, namely the sFlt-1/PlGF ratio. We feel that this may help clinicians to differentiate the fetus that is constitutionally small from that which has a reduced growth velocity due to placental failure. Identifying the group at highest risk of stillbirth would reduce the number of Interventions performed, and reduce the number of babies delivered early whilst maintaining a safety

margin to prevent stillbirth. This would represent a more detailed monitoring system than any other nation currently advocates.

1.3 Review of existing evidence

The use of biomarkers to identify the fetus at risk of stillbirth has been highlighted as a priority by the RCOG [18] and the James Lind Alliance [34]. However, their low predictive accuracy in the first trimester has limited their use as a screening tool [3]. Recent advances in our understanding of which biomarkers are clinically relevant in late pregnancy has demonstrated that identification of placental disease potentially predisposing to stillbirth is possible [35]. Principal among the biomarkers currently available is placental growth factor (PlGF). This protein is produced by the placenta and identifiable in maternal blood from 12 weeks [36]. Two commercially available platforms which measure PlGF (Alere®) [37] or PlGF relative to sFlt-1 (sFlt-1/PlGF ratio) (Roche®) [38] have been endorsed by NICE for the investigation of hypertension in pregnancy [39].

Whilst the majority of studies have focussed on the ability of these tests to predict preeclampsia there is a significant amount of information on their ability to predict stillbirth and SGA. Abnormally low levels of PlGF in maternal plasma have been linked to preeclampsia [37, 40, 41], SGA [42, 43] and stillbirth [37, 44]. Furthermore, an abnormal PlGF appears to more than double adverse pregnancy outcome [45] and is associated with critical fetal growth restriction [46-50]. In a cohort of SGA fetuses, low PlGF was associated with preterm delivery, stillbirth, birth weight <3rd centile, apgar <7 at 5 mins, NICU admission and placental pathology [37, 51, 52]. Women with the lowest PlGF values were in addition much more likely to have a growth restricted fetus and abnormal Dopplers [37, 44]. In all published studies to date very few fetuses have been stillborn following a normal PlGF result [56-59]. The ratio of PlGF to soluble FMS-like tyrosine kinase-1 (sFlt-1), which binds PlGF in the circulation, is increased in preeclampsia [38], fetal growth restriction [53] and stillbirth [54]. An abnormal sFlt-1/PlGF ratio of **≥**38is associated with an increased risk of SGA (21% vs 7%) [55]. The sFlt-1/PlGF ratio appears to be equally useful in determining outcome with almost no stillbirths when the ratio is normal [38, 55-57] (Table 1 and Figure 2). A recent Cochrane Diagnostic Test Accuracy Review on the effectiveness of biomarkers to predict stillbirth [65] confirms that abnormal PlGF or sFlt-1/PlGF ratio has a diagnostic odds ratio of 49.2 for subsequent stillbirth (personal communication) (Figure 2).

Therefore, PlGF or sFlt-1/PlGF ratio appear to be effective in identifying the fetus that is SGA and more importantly, those fetuses that go on to be stillborn. Roche® have agreed to provide financial assistance to this study by providing the sFlt-1/PlGF ratio kits for no cost. In addition, Perkin-Elmer® who also

produce a commercial PlGF assay and Quidel® (new owners of the Triage PlGF platform formerly owned by Alere®) have agreed to support the application by providing further testing of PlGF on their platform, for no cost, during the study. The results of the Perkin-Elmer® and Quidel® tests will not be used to influence the care pathway.

Figure 2: ROC curve of stillbirth related to diagnostic test. PlGF (green) shows the greatest sensitivity for subsequent stillbirth [58]. Personal communication Prof A Heazell (University of Manchester).

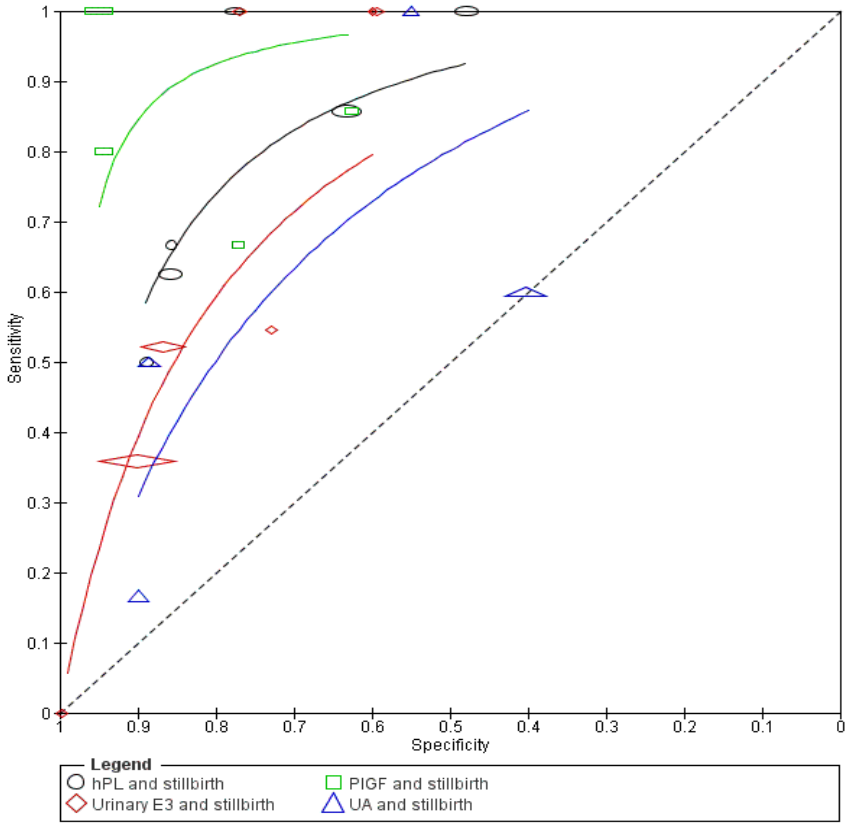


Table 1: Stillbirths by normal and abnormal PlGF and sFlt-1/PlGF ratio

Author	Year	Stillbirth normal PlGF	Stillbirth abnormal PlGF	Stillbirth normal sFlt-1/PlGF ratio	Stillbirth abnormal sFlt-1/PlGF ratio
Chappell	***2013***	0	7	-	-
Benton	***2016***	1	6	-	-
Ziesler	***2016***	-	-	1	3
Sovio	***2017***	-	-	0	0
Sharp (1)	***2018***	0	1	-	-
Sharp (2)	***2018***	0	35	0	35
Navaratnam	***2017***	0	1	0	1
Total		1	50	1	39

The overall aim of this study is to assess the feasibility of conducting a larger, definitive RCT to determine the effectiveness of using the sFlt-1/PlGF ratio to refine SGA pregnancy management pathways. A mixed method approach has been adopted including a pilot trial and qualitative research with women and clinicians to address the following objectives.

1.4 Study Objectives

The PLANES study has the following overall objectives:

- To assess the feasibility of delivering sFlt-1/PlGF ratio led management of women with an SGA fetus
- To assess the acceptability of such an approach to women and clinicians
- To explore the feasibility/acceptability of the study design as an external pilot to inform the design of a subsequent randomised controlled trial (RCT)

1.5 Potential Risks and Benefits

The potential risks and benefits of involvement are detailed below.

1.5.1 Potential Risks

Potential risks of participation would be an adverse pregnancy outcome in women with an SGA fetus and a normal sFlt-1/PlGF ratio. In this protocol women will be delivered later than would currently be offered under NHS care. To mitigate any potential risks women will be offered repeat ultrasound and

sFlt-1/PlGF assessment every 2 weeks. If there are new concerns on ultrasound or the sFlt-1/PlGF ratio becomes abnormal then care will be adjusted.

1.5.2 Potential Benefits

This study has the potential benefit of reducing the likelihood of intervention in women carrying a SGA baby with a normal sFlt-1/PlGF ratio. This may allow normalisation of labour, less medicalisation of care and greater control and choice for women as to the time of delivery than is currently offered. In addition in those women with an abnormal sFlt-1/PlGF ratio there will be greater recognition of clinical concern and more detailed ultrasound assessment will be performed which may improve the outcomes for the most high risk pregnancies. Reducing the number of pre-term and early term deliveries is also expected to result in reduced need for costly short and long-term care required by preterm and SGA infants.

2. STUDY DESIGN

This study is a randomised controlled study of pregnant women with an ultrasound diagnosis of an SGA fetus (defined as having an EFW < 10^{th} percentile for gestation) with normal umbilical artery waveform assessed in the preceding 72hrs at 32^{+0} to 37^{+6} weeks' gestational age (wGA). Participants will be recruited directly from the fetal medicine or maternity assessment units at the nominated research sites. All women who meet the eligibility criteria for this study will be invited to participate by their attending clinician and / or midwife. Once written informed consent has been provided participants will be registered onto the study and randomised by the research midwife / clinician at site.

Following randomisation women will be asked to provide a blood sample (25ml) for assessment of sFlt-1/PlGF ratio, the result of which will be revealed (biomarker led) or concealed (standard care) from the attending clinician. An sFlt-1/PlGF ratio measurement will be carried out within the local NHS laboratory as per local procedure, with the result being available to the attending clinical team within 24 hours.

Within the revealed / biomarker led care group participants with a normal sFlt-1/PlGF ratio (<38) will be advised that their risk of an adverse pregnancy outcome is low and will be offered delivery at 40^{+0} wGA. Women will be offered further ultrasound, cCTG and sFlt-1/PlGF ratios every 2 weeks, to ensure that they do not become high risk, with the care pathway adjusted if necessary (see Figure Two). Participants with an abnormal sFlt-1/PlGF ratio (≥38) will be advised to attend for detailed ultrasound assessment by a fetal medicine expert within 72hrs of the abnormal result being known, unless already performed on the day of sFlt-1/PlGF testing. This assessment will involve Dopplers of the Umbilical Artery (UA), Uterine artery (UtA), Middle Cerebral Artery (MCA) and Ductus Venosus (DV). If Dopplers

are normal then delivery will be advised from 37^{+0} weeks [22]. cCTG will be performed once per week with Dopplers repeated as per pathway with biometry every two weeks.

If there is evidence of critical fetal compromise (absent end diastolic flow in the UA or absent a-wave in the DV) then delivery will be performed as soon as feasible. If fetal Dopplers are borderline (brain sparing or increased resistance in UA or DV), the Doppler will be repeated every 72hrs and delivery will be offered between 36^{+0} and 37^{+0} weeks. cCTG will be performed once per week.

Women assigned to the concealed / standard care pathway will have an sFlt-1/PlGF ratio taken but the result will be concealed from the clinical team with their pregnancy being managed as per the local NHS guideline with delivery from 37^{+0} weeks.

Once recruited, all participants will remain in the study until discharge from hospital or their due date whichever is sooner. We will collect routine clinical data from all participants' notes and electronic hospital records for maternal and neonatal outcomes.

Women who prefer not to be randomised will be offered the opportunity to give blood for an sFlt-1/PlGF ratio test and research bloods with the result being concealed and not used to guide clinical management. Results from this pilot study along with health economic and qualitative elements will inform the design of a future large randomised controlled trial powered for adverse pregnancy outcome.

2.1 Outcome Measures

This study will assess the feasibility of using a blood biomarker, sFlt-1/PlGF ratio, to safely refine the care pathway for the management of women with an SGA fetus from 32 weeks of pregnancy.

No formal power calculation or primary outcome data has been determined. Success of the study will instead be determined on the acceptability of the study for women and clinicians. This will be determined by an ability to recruit and retain participants within the study.

3. STUDY POPULATION

3.1 Pre-Registration / Randomisation Procedures

All women will be recruited directly from the fetal medicine or maternity assessment unit. Prior to taking part in the study all women will have confirmation of their SGA status completed by their attending clinician based on an ultrasound scan performed within the preceding 72 hours.

3.2 Inclusion Criteria

The following inclusion criteria for this study will be adopted.

- Women with an SGA fetus between 32^{+0} and 37^{+6} weeks of gestation.
- Singleton pregnancy
- Age ≥16 years
- EFW <10th centile on ultrasound within preceding 72hrs
- Normal Umbilical Artery Doppler (defined as present End Diastolic Flow (EDF) and Pulsatility Index (PI) within the normal range for gestation)

3.3 Exclusion Criteria

The following exclusion criteria for this study will be adopted.

- Unable to give informed consent
- Known or suspected structural / chromosomal fetal abnormality
- Absent or reversed EDF in Umbilical Artery on Doppler study
- Severe maternal disease requiring urgent delivery

3.4 Withdrawal Criteria

We do not have formal stop criteria for a short study such as this. However, we will establish an Independent Safety and Data Monitoring Committee (ISDMC) which will meet six months into recruitment and will have the authority to recommend to the Trial Steering Committee (TSC) to stop recruitment should there be concerns about patient safety.

In consenting to take part in the study, participants are consented to the study intervention, sample gifting, potential participation in qualitative sub-study, data collection and follow-up. If voluntary withdrawal occurs, the participant should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care until delivery.

The critical data in the PLANES study is derived from blood samples. Although participants can refuse a blood sample at any time, refusal to give crucial samples (following randomisation) would result in significant compromise to the study. Therefore, any participant who does not provide this sample would need to be withdrawn from the study.

Foreseeable reasons where a participant may withdraw from the study generally apply to the taking of

study blood samples and include:

- Participant withdraws consent,
- Participant is unable to make regular assessments,
- Loss of capacity during the study, and
- Any other change in the participant's condition that justifies the discontinuation in the clinician's opinion.

A participant is free to withdraw from the study at any time. In addition, the Chief Investigator (CI) may decide, for reasons of medical prudence, to withdraw a participant. In either event, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the participant source data. If a participant withdraws or is withdrawn ideally they should remain in the study for the collection of safety data and/or treatment of any AEs, until these have resolved. Generally, follow-up will continue unless the participant explicitly also withdraws consent for follow-up. The CI may also request that the participant return for an additional follow-up visit, for the purpose of collecting safety data, or ensuring resolution/adequate treatment of an AE.

Participants who withdraw from the study for other reasons have previously consented to follow-up in the study. Data up to this time can be included in the study if anonymised. Each participant may need to reaffirm consent to follow-up through usual NHS mechanisms. If the participant explicitly states their wish not to contribute further data to the study, a withdrawal electronic Case Report Form (eCRF) should be completed.

3.5 Patient Transfers

For participants moving from the area, every effort should be made to encourage them to remain part of the study. Such circumstances will be dealt with on a case-by-case basis.

3.6 End of Study

The study will end when all associated study samples and data have been collected and analysed as part of the overall objectives of the research.

3.7 Stopping Criteria

The need to stop the study will be determined by the Study Oversight Committees. The decision will be based upon participant safety. If any of the following scenarios occur with reasonable possibility of a

causal relationship with the study intervention, the Study Oversight Committees will review and advise whether continuation of the study is recommended:

- Clinically relevant signs or symptoms or intolerable adverse events of similar nature occurring in 2 or more participants that in the opinion of the CI warrant stopping
- One or more participants report a serious adverse event considered by the CI, local Principle Investigator (PI), or delegated other physician who can assess causality and expectedness of AEs to be at least possibly related to the study intervention.

4. ENROLMENT AND RANDOMISATION

4.1 Participant Selection

All participants will be recruited from their local fetal medicine or maternity assessment unit. They will be contacted in person by a member of the core clinical research team (PI / research midwife) and invited to take part in the study. At this point participants will be given written and verbal information on the PLANES study, as well as an opportunity to ask questions. All potential participants will be given a unique screening ID that will subsequently be used to detail the reasons for the continuation or discontinuation at the screening stage.

4.1.1 COVID-19 Precautions

Research sites should follow standard local and NHS policies to reduce the risk of COVID-19 infection. These include asking staff and study participants to use alcohol hand gel, observe social distancing where possible and wear a face covering. Paper masks should be available and handed out at the hospital entrance should they be required for visiting participants. Visitors to the research site may also have a temperature check prior to entry.

Participants at research sites may be required to have a swab test for COVID-19. The result of the swab test may not be known at the time of consent for this study. This should not prevent consent from being obtained. Should the swab result be positive for COVID-19, the participant will remain within the study unless participation in the study would be detrimental to their care. If withdrawn from the study any samples that may have been taken will be destroyed and no further samples will be taken. Any research data that has been recorded will not be included in the analysis of this study and no further data will be collected.

Site staff are required to wear medical facemasks, disposable aprons and gloves whilst they care for study participants, regardless of the COVID-19 swab result.

4.2 Consent

Once a potential participant has been identified, a member of the clinical research team at site will discuss their potential participation. Participants will be given written and verbal information on the PLANES study and provided with the opportunity to ask questions and take any additional time required to consider taking part in the study. Following this, participants will be asked to sign the study-specific Informed Consent Form (ICF) in the presence of the site researcher, for whom a signature is also required. Three copies of the participant consent forms will be collected, the original should be given to the participant, one should be held in the site file and the final copy should be send to the Research / Trial Manager at the) Harris Research Centre. The site PI is also required to review and sign all consent forms.

4.3 Enrolment / Registration and Baseline

Once eligibility has been confirmed by the PI at site the participant will be registered and then randomised onto the study using an electronic registration platform. Although it will be recommended that participants take a minimum of 24 hours to consider taking part in this study, the provision for allowing participant consent within a shorter period of time must be permitted, as the nature of the condition often requires prompt intervention. Documentation of reasons for non-inclusion will be detailed in the site screening logs and forwarded to the Research Manager at the Harris Research Centre.

Once a participant consents to taking part in the study, they will be registered and randomised on a bespoke electronic data capture system that will generate a unique participant identification number.

5. STUDY INTERVENTION

5.1 Detailed Study Procedure

Following randomisation women will be asked to provide a blood sample for assessment of sFlt-1/PlGF ratio, the result of which will be revealed (biomarker led) or concealed (standard care) from the attending clinician. sFlt-1/PlGF ratio assessment will be performed within NHS laboratories with a 24-hour turnaround time as any future clinical use would require these facilities. Women with a normal sFlt-1/PlGF ratio (<38) will be advised that they are low risk and will be offered delivery at 40^{+0} weeks with further ultrasound and sFlt-1/PlGF ratio's taken every 2 weeks with the care pathway adjusted if necessary. An

abnormal sFlt-1/PlGF ratio (≥38) will necessitate detailed ultrasound assessment by a fetal medicine expert within 72 hours, if not performed at the time of enrolment. This assessment will involve fetal biometry and Dopplers. If the Dopplers are normal then delivery will be advised from 37^{+0} weeks [18]. If there is evidence of critical fetal compromise (absent end diastolic flow in UA or absent a-wave in DV) then delivery will be performed as soon as feasible. If fetal Dopplers are borderline abnormal (brain sparing or increased resistance in UA or DV) Doppler will be repeated every 72 hours and delivery will be offered between 36^{+0} and 37^{+0} weeks (see Figure 3 Participant Management Pathway).

Pathway 1	**Randomised - Standard care (Control arm) - sFlt-1/PlGF ratio <u>Concealed</u>**
• Return to routine care • cCTG and USS only as per local guideline • sFlt-1/PlGF Ratio and Research bloods at enrolment only • Offer delivery from 37^{+0} weeks [22]	

Pathway 2	**Randomised - Biomarker led care (Intervention arm) - sFlt-1/PlGF ratio <u>Revealed</u>**
Pathway 2a	**sFlt-1/PlGF ratio result normal (<38)**
• Reassure • Reassess sFlt-1/PlGF ratio and ultrasound every 2 weeks (if abnormal change to pathway 2b, If normal offer delivery at 40^{+0} weeks) • Research bloods at enrolment only • cCTG every 2 weeks	
Pathway 2b	**sFlt-1/PlGF ratio result abnormal (≥38)**
• cCTG every week • No further sFlt-1/PlGF ratio or research bloods • Fetal medicine ultrasound scan for EFW, liquor, UA, MCA and DV Doppler within 72hrs of abnormal result (if not performed at the time of enrolment) - *Normal scan - offer delivery from 37+0 weeks and weekly US scan [18]* - *Borderline scan (raised PI in UA or DV, or brain sparing evident in MCA) - offer review every 72hrs with US scan and delivery between 36+0 and 37+0 weeks* - *Abnormal scan (critical fetal compromise: absent EDF in UA or absent a-wave in DV) – offer delivery as soon as feasible*	

Pathway 3	Observational Only
• Routine care • Single sFlt-1/PlGF ratio at enrolment • Offer delivery as per local clinical team	

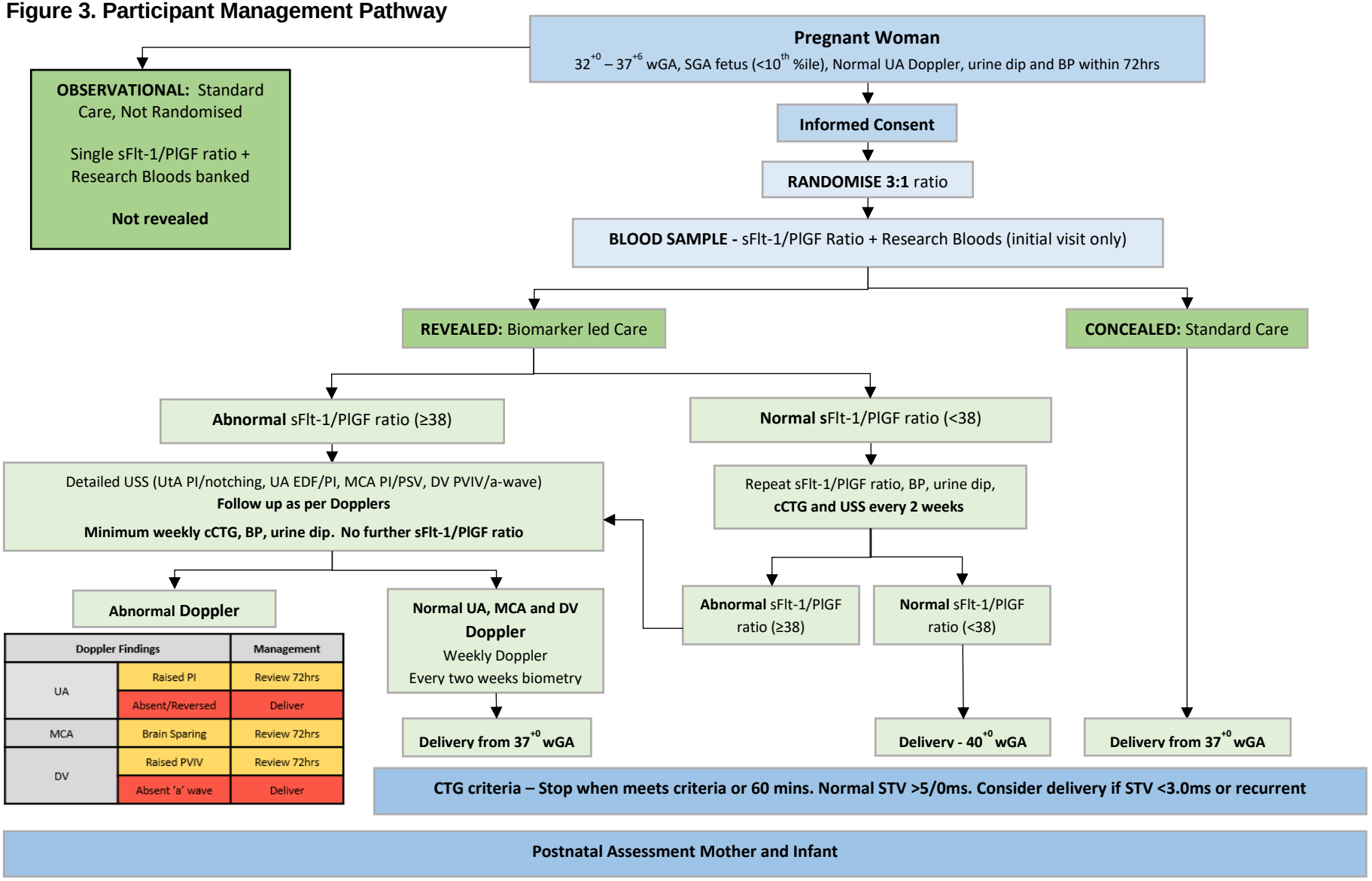
All cases women on pathway 2a or 2b will receive computerised cardiotocography (cCTG) on the same day as ultrasound assessment and a minimum ofevery two weeks (pathway 2a). or weekly (pathway 2b), or more frequently if the local team requires. If at any point cCTG demonstrates a short-term variability (STV) <3.0ms then delivery should be planned [59]. If at any point the attending clinical team feels the need to deviate from this care pathway they will be able to do so, with outcomes recorded on an intention to treat basis.

We are conscious that women may not feel that they should deviate from 'normal' NHS care despite the more detailed assessments of fetal wellbeing we have set in place. In order to increase the ability of this study to inform a future RCT powered to prevent stillbirth we will ask women who decline to be randomised whether they would consent to a single sFlt-1/PlGF ratio and research bloods being taken and stored for processing only after the study has ended (pathway 3). In this way we may still gain valuable information about the ability of this test to predict clinically relevant pregnancy outcomes even if women do not wish to be randomised. This approach has been supported by our PPI.

Comparator

The comparator will be women with an SGA fetus managed as per normal care (randomised to control arm, pathway 1 or non-randomised (observational arm) pathway 3) [18]. Further comparison will be drawn between those with a normal sFlt-1/PlGF ratio and those with an abnormal sFlt-1/PlGF ratio.

Figure 3. Participant Management Pathway



Doppler Findings		Management
UA	Raised PI	Review 72hrs
	Absent/Reversed	Deliver
MCA	Brain Sparing	Review 72hrs
DV	Raised PVIV	Review 72hrs
	Absent 'a' wave	Deliver

5.2 Co-enrolment Guidelines

Participant enrolment in other research studies should not take place unless consultation with the site PI has confirmed that this poses no additional risk to patient safety or affects the quality of the PLANES study data.

5.3 Concomitant Medications / Procedures

Any medications that are taken and / or medical procedures / interventions that take place at the time of participation in the PLANES study will be detailed for each participant on the electronic Case Report Form by the site research staff.

6. ASSESSMENTS AND PROCEDURES

6.1 Schedule of Study Procedures

Participants will remain in the study for a maximum of 8 weeks (from 32+0 weeks [earliest point of eligibility] to EDD). Following the completion of eligibility checks and the provision of written informed consent, participants will be registered onto the study and randomised. This will be followed by the provision of a blood sample which will be collected at randomisation. This blood sample will be collected by the site research clinician and sent immediately for processing to the local hospital laboratories. Following randomisation and blood sampling participants will follow their relevant pathway (as detailed previously in Section 5.1).

6.2 Total Blood Volume Collected

The maximum blood volume to be taken per participant will not exceed 100ml over the 8 week period (maximum of 4 blood sampling time points of 25ml at enrolment (sFlt-1/PlGF ratio and research bloods and then sFlt-1/PlGF ratio only at each subsequent timepoint depending on pathway). The laboratory procedures for each time point will be detailed in a separate PLANES Laboratory Management Plan.

6.3 Clinical Procedures

The timings of all measurements to be performed during the course of the study may be subject to change based on an ongoing review of study procedures. All changes will be agreed with the Sponsor and documented in the Study Management Folder (SMF).

6.4 Adverse Events

The condition of each participant will be monitored throughout the study, from the time of informed consent through to one-month post-delivery. Participants will also be encouraged to report adverse events occurring at any other time during the study. Any adverse event as detailed in this protocol will be recorded in the participant source data and the study eCRF. The nature, time of onset, duration and severity will be documented together with the Investigators opinion of the relationship to the study intervention. Any clinically significant events identified during the course of the study will be followed up until they are resolved or can be clinically explained. Adverse Event (AE) definitions, assignment, causality and procedures for reporting Serious Adverse Events (SAEs) are detailed in Section 8 of this protocol and in the PLANES Safety Plan. All AEs for this study will be described using the MedDRA coding system (version 24.1).

6.5 Vital Signs

Semi-recumbent blood pressure, pulse rate and urine dip test for proteinuria will be measured at the time indicated on the study schedule. Vital signs will also be performed at other times if judged clinically appropriate, if required by hospital policy or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

6.6 Clinical Laboratory Assessments

Blood will be collected as part of standard care for clinical laboratory evaluations at times indicated in the schedule. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate, required by hospital policy (MRSA) or if ongoing review of the data suggests a more detailed assessment of the clinical laboratory safety evaluation is required. An investigator will perform a clinical assessment of all clinical laboratory data.

Research bloods will only be taken at enrolment (See Laboratory Manual).

6.7 Maternal Assessments

Blood pressure and pulse will be checked at each visit when sFlt-1/PlGF blood samples are taken. At each visit urine should also be assessed on dip test for the presence of proteinuria.

6.8 Fetal Assessments

The initial ultrasound to confirm eligibility may be performed by an ultrasonographer, midwife

sonographer or medical staff. The same staff groups can also perform further follow up scans in the concealed or revealed normal sFlt-1/PlGF ratio arm. If there is concern about the accuracy of an ultrasound assessment this should be confirmed by the site PI. In those women with an abnormal sFlt-1/PlGF ratio all scans should be performed by appropriately trained medical staff under the supervision of an expert in fetal medicine.

Computerised CTG should also be performed a minimum of once every two weeks for all women in both the concealed and revealed arms (sFlt-1/PlGF ratio <38) (Pathway 2a) and a minimum of weekly in revealed arms (sFlt-1/PlGF ratio ≥38) (Pathway 2b). In all cases delivery should be considered if there is an STV <3.0ms.

Women on Pathway 1 (randomised to routine care) or 3 (non-randomised, observational) will have fetal assessment with CTG and USS as per local guidelines.

6.9 Other Assessments

6.9.1 Special Laboratory Procedures

All information relating to laboratory analyses and procedures employed within this study will be detailed in a separate PLANES Laboratory Management Plan. This will include instruction for the preparation, handling, storage and shipping of samples including required temperatures, aliquots of samples, where they will be stored and how they will be tracked and labelled. All procedures will be detailed in separate protocols / Work Instructions (WI) which will be included in the Laboratory Management Plan together with plans in terms of the long-term access and consent for the future use of samples.

sFlt-1/PlGF appears to be the most accurate biomarker currently available to assess the health of the placenta and by inference the health of the fetus. An abnormal sFlt-1/PlGF ratio has been associated with fetal growth restriction, abnormal fetal Dopplers and stillbirth. The sFlt-1/PlGF ratio, manufactured by Roche, will be used to guide intervention in the study. This decision was taken as at the initial submission of this project it was the only commercially available biomarker test endorsed by NICE for the assessment of placental function, in the context of diagnosis of preeclampsia.

Since the initial application, other companies have also begun to produce PlGF biomarker tests. We have agreement from two such companies, Perkin-Elmer and Quidel, to perform post-hoc analysis of blood samples from women recruited to the PLANES study to assess whether they are also able to be used in the future management of SGA. Neither of these tests will however be used to determine clinical care pathway during the study period.

In order to get the most information possible during the study period to inform the future management of SGA pregnancies we will be asking women to allow us to use the remaining blood taken during PLANES to be used in other ethically approved research, a process called “gifting”. This further assessment may involve as yet, unknown biomarker or genetic testing.

6.9.2 Shipment of Samples

Experimental blood samples relating to the intervention pathway collected at Liverpool Women’s Hospital and St Mary’s Hospital will be analysed within the Liverpool Clinical Laboratories at the Royal Liverpool and Broadgreen University Hospital NHS Trust and the Manchester University NHS Foundation Trust, respectively. Samples will be transported using the standard NHS internal pathway that will be agreed in a formal Service Level Agreement.

Additional samples that will be collected from both sites will be sent to the Centre for Women’s Health Research laboratories where they will be processed and stored until the end of the study. All samples will be subject to a study specific Material Transfer Agreement (MTA). Details of sample transportation can be found in the PLANES Laboratory Management Plan.

At the end of the study it may be beneficial to send samples to other laboratories for specialised analyses to be performed. These samples would be used for exactly the same purposes as outlines above in section 6.9.1. Permission to send material to other laboratories, and the parameters of the purpose of this, will be included in the Participant Information Sheet (PIS) and ICF.

6.9.3 Storage of Samples

Samples gifted as part of the study, if they are not used in meeting the scientific objectives, will be stored for a period of 25 years. The samples can be used in future studies addressing research into identifying biomarkers for prenatal risk, but not for other purposes. An example of such a use might be the use of stored samples in assessing the relevance of a newly discovered biomarker.

6.10 Loss to Follow up

If for any reason a participant does not complete the study they should attend a final visit / assessment with the site investigator as soon as possible. If the study intervention is stopped before the end of the scheduled assessment period, the clinician may contact the participant to request additional information up to the point where the study intervention would be completed.

6.11 Study Closure

Investigators will be informed when recruitment is to stop. Study enrolment may be stopped at a site when the total requested number of participants for the study have been recruited. The Study Oversight Committees may recommend that the study be stopped prematurely. In such circumstances of premature termination / suspension of the study, the National Research Ethics Committee (REC) and Health Research Authority (HRA) will be notified according to the standard reporting guidelines.

Table 2. Schedule of Study Related Procedures

Procedure		*Screening	*Baseline	Study Visit 1	Study Visit 2	Study Visit 3	Delivery	Postnatal	End of Study
Global Outcomes									
Review of Medical History		X							
Review of Medication		X							
Maternal Assessment	*Blood Pressure*	X		X	X	X			
	Pulse	X		X	X	X			
	Urine Dip	X		X	X	X			
Fetal Assessment	*Ultrasound Scan*	X							
Eligibility Assessment		X							
Informed Consent			X						
Randomisation			X						
Blood Sample Collection			X	X	X	X			
Qualitative: Women / Partner			X						X
Qualitative: Clinician									X
Health Economic: EQ-5D-5L			X				X		
Health Economic: CEQ							X		
Delivery Outcomes							X		
Maternal Postnatal Outcomes								X	
Neonatal Postnatal Outcomes								X	
End of Study Outcomes									X
¥Concealed (Randomised) - Standard Care Pathway 1									
Adverse Event Reporting									X
Collection of standard care outcomes									X
ǂRevealed (Randomised) – Normal Group Pathway 2a									
Maternal Assessment	*BP*			X	X	X	X	X	
	Pulse			X	X	X	X	X	
	Urine Dip			X	X	X			
Fetal Assessment	*cCTG*		X						
	Ultrasound (every 2 weeks)			X	X	X			
	cCTG (every 2 weeks)			X	X	X			
Adverse Event Reporting				X	X	X	X	X	X
Blood Sample Collection				X	X	X			

Table 2. Schedule of Study Related Procedures continued

Procedure		*Screening	*Baseline	Study Visit 1	Study Visit 2	Study Visit 3	Delivery	Postnatal	End of Study
≠***Revealed (Randomised) – Abnormal Group Pathway 2b***									
Maternal Assessment	*BP*			X	X	X	X	X	
	Pulse			X	X	X	X	X	
	Urine Dip			X	X	X			
	cCTG		X						
Fetal Assessment	*Ultrasound*			X	X	X			
	cCTG (weekly)			X	X	X			
	Doppler			X	X	X			
Adverse Event Reporting				X	X	X	X	X	X

¥***Observational Only (non-randomised) - Pathway 3***								
Adverse Event Reporting								X
Collection of standard care outcomes								X

* for some participants the decision to take part in the study may be within 24 hours, in such circumstances baseline assessments / procedures will take place at randomisation

¥ Participants to be managed as per local standard practise

‼ Study Visits to take place every 2 weeks up to delivery or 40 +0 wGA

≠ Study Visits to take place every week dependent on Dopplers up to delivery from 36 +0 wGA

7. STATISTICAL CONSIDERATIONS

7.1 Introduction

In the following section a brief overview of the planned analyses for this study will be set out. Further analysis plans are provided separately from this document in a study specific Statistical Analysis Plan (SAP) which will include information on all aspects of analysis for this study (including Health Economics and Qualitative work packages). Both this protocol and the SAP will be formally approved by the Study Oversight Committees. The SAP will be developed and available within 4 months of the study opening to recruitment.

Participants will be registered onto the study database and then randomised in accordance with the study registration / randomisation operating procedures. Participants will be randomised to receive revealed or concealed pathways in a ratio of 3:1. Patients will be randomised by authorised site staff using an electronic randomisation system. This system will be available 7 days per week, 24 hours a day and will be accessed by delegated site staff using a secure password protected website. All site staff will receive comprehensive training on the use of this system, which will be documented and stored in the Investigator Site File (ISF).

In the unlikely event that the back-up registration / randomisation process is activated, participant registration and randomisation will be performed by the Research Manager or LCTC Information Security (IS) staff

The randomisation code list will be generated on the basis of randomly permuted blocks by an LCTC statistician other than the study statistician using the 'ralloc' command with the software package STATA. LCTC IS staff at the University of Liverpool will be responsible for designing and supporting the PLANES randomisation program. The documentation required to recreate the randomisation (i.e., code list and seed number) will be stored in the IS section of the PLANES SMF.

Data from the PLANES workbooks / CRFs at site will be entered onto a bespoke study database with extensive data validation checks alerting all missing data to be queried. Missing data will be monitored and strategies will be developed to minimise its occurrence. Central statistical data monitoring will summarise missing or inconsistent data periodically. The study workbook will be approved by the CI and validations will also be made that will cross check the study workbook with the PLANES eCRF.

7.2 Outcome Measures

This study will assess the feasibility of using a blood biomarker (sFlt-1/PlGF ratio), to safely refine the care pathway for the management of women with an SGA fetus from 32^{+0} weeks of pregnancy. No formal power calculation or primary outcome data will be determined. Success of the study will instead be determined on the acceptability of the study to women and clinicians. This will be determined by an ability to recruit and retain participants to the study.

7.2.1 Women, Partner and Clinician Perspectives

7.2.1.1 Design

The PLANES study will involve an integrated mixed methods element, including interviews and questionnaires with women and their birth partners (if applicable), as well as a focus groups with clinicians involved in the study. Individual interviews and an online survey will also be conducted with clinicians unable to attend the focus group. These study elements will aim to explore women's, birth partner's (if applicable) and clinician's views on,

- the approach to recruitment in the PLANES study, including consent, decision making and length and content of study information materials, and
- the acceptability of a future trial, including potential barriers to recruitment, consent decisions, trial procedures and clinician training needs.

Interviews and questionnaires with women and their birth partners will be conducted with those who consent and decline to participate in the study as well as those with relevant experience recruited via social media adverts. We will sample to ensure that both groups of women (abnormal sFlt-1/PlGF ratio and normal sFlt-1/PlGF ratio) are represented. Interviews will be conducted until data saturation point, this is when major themes identified in the analysis of new data are reoccurring from previous participants / transcripts, and no new major themes are being discovered. Based on previous similar pilot studies, this is anticipated to be 15-25 interviews. We expect to receive approximately 50 questionnaires (48% response rate) from women.

We will also conduct a focus group with (n=~9) clinicians involved in the study. Focus groups will incorporate the use of voting software so that both qualitative and quantitative data are collected. Interviews and an online survey will be carried out with any clinicians unable to attend the focus group.

7.2.1.2 Selection of Participants

Women and birth partners at participating sites: All women and birth partners (if applicable) will be sampled as per inclusion criteria. The PLANES PIS will include information regarding taking part in this qualitative work package (WP). If women are happy to take part in this WP, they will be asked to complete the relevant sections of the study ICF. Women who do not agree to take part in the main study will also be asked if they would like to take part in this qualitative WP. Information regarding this will be detailed on the PLANES PIS. These participants will be expected to complete the standard participant ICF, however the researcher at site should ensure that they initial only those boxes that are relevant to taking part in the qualitative study.

Women and their partners (if applicable) will be asked to consent to whether they would like to complete a questionnaire and / or take part in a face-to-face or telephone interview discussing their views on the proposed trial. For women / partners who agree to take part in this WP, their personal contact information will be detailed on the PLANES Confidential Participant Contact Information form by site research staff and forwarded to the Research Manager. This information will be collected at the same time as the participant ICF and will be managed using an identical secure process. Once received and validated, the Research Manager will provide the contact information to the Qualitative Researcher (in a secure manner) who will then make direct contact with the participant(s).

Women and birth partners through social media: The PLANES qualitative research team will advertise the study on social media platforms (e.g. Twitter, Facebook) using the PLANES social media advert. The advert will contain information and contact details of the researcher for parents to register their interest in taking part in an interview.

Clinicians: Clinicians involved in the PLANES study will be sent an email invitation to participate in a focus group (approximately 8-10 participants). Email addresses will be collected at the point of Site Feasibility / Greenlight and will be stored on the study Trial Management System (TMS) as per standard protocol. Information regarding this part of this study will also be presented during the Site Initiation Visit (SIV). Written consent will be sought from clinicians before the focus group begins. This will also include consent for digital audio recording of the group discussion.

Those unable to attend the focus group will be invited to participate in an interview and an online questionnaire. The introduction to the online questionnaire will explain how completion of the questionnaire will constitute consent for participation.

Participation will be voluntary and participants will be able to withdraw at any time without giving a reason.

7.2.1.3 Eligibility

Inclusion criteria

- Women (and partners) who consent to the PLANES study
- Women (and partners) who consent only to take part in the qualitative work package of the PLANES study
- Women (and partners) whose baby was small for gestational age in the womb within the last three years
- Clinicians who are involved in screening, recruiting, randomising and consenting women as part of the PLANES study

Exclusion criteria

- Women (and birth partners) who do not speak English

7.2.1.4 Procedures

Women and partner questionnaires

Following the provision of informed consent to the qualitative work package, a delegated member of the site research team will provide the PLANES Qualitative Questionnaire to each women and their partner (if applicable) to complete. This questionnaire will be provided to women and their partners to be completed independently. They will be able to complete this at site during their clinic visit or they can take it home with them and complete it in their own time. For participants who complete the questionnaire at site, the questionnaire will be returned to the site staff who will forward it to the Research Manager at the Harris Research Centre using either secure email to PLANES@liverpool.ac.uk or faxed to **0151 795 9599**. Participants will also be permitted to take this questionnaire home to complete. These participants will be provided with an addressed and pre-paid envelope to return the questionnaires. Please note – a preference will be made for participants to complete the questionnaire at site.

Women and birth partner interviews

For those recruited through sites: The PLANES Qualitative study team will make contact with women and their partners to arrange an interview within approximately one month of consent.

For those recruited through social media: The researcher will check eligibility and send a PIS to all who register interest in participating. The RA will then arrange a suitable time for an interview. Those who do not meet the eligibility criteria, or register after the target sample size (15-25 depending upon data saturation point) has been reached, will be thanked for their time and will take no further part in the study.

Consent for interviews: The RA will begin the telephone interview by explaining the aims of the study, providing an opportunity for questions and verbally obtaining informed consent for the study. This will involve the researcher reading each aspect of the PLANES Interview Participant Consent Form to participants, including consent for audio recording and to receive a copy of the findings when the study is complete. The researcher will tick each box on the consent form when the participant provides verbal consent. Informed consent discussions will be audio recorded for auditing purposes.

Interview conduct: Face-to-face interviews will be offered in the first instance although telephone interviews will be provided as an option if preferred by the participant. All interviews will be conducted by the team using the PLANES women and partner interview topic guide. Consent for audio recording of the interview will be checked before the interview commences and is recorded by the qualitative researcher. The topic guide used within this study has been informed by previous pilot trials conducted in the NHS. Respondent validation will be used so that previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress.

Any distress during the interviews will be managed with care and compassion. Participants will be free to decline to answer any questions that they do not wish to answer or to stop the interview at any point. Following on from this, such individuals will be supported in obtaining appropriate help via the standard NHS pathway.

After the interview is complete, participants will be sent a letter and a £30 Amazon® voucher to thank them for their time. All women and partners who express an interest in taking part but are not selected for an interview will be contacted via email or by postal letter to thank them for their interest in the study.

Clinician focus group

For clinicians taking part in the focus group, this will take place in a meeting room at the study site at

the end of the PLANES study recruitment period. The groups will be facilitated using a voting software package (TurningPoint Technologies). TurningPoint is an easy-to-use engagement and assessment system that allows researchers and participants to respond confidentially, in real time using their own device. A variety of interactive polling options are available to meet the unique needs of the study. All focus groups and interviews will be conducted by the University of Liverpool PLANES Qualitative study team using the clinician focus group and interview topic guides. The topic guides will be informed by interim findings from women and birth partner questionnaires and interviews. After the focus group or interviews are complete, clinicians will be sent a thank you letter.

Clinician Interview: Clinician interviews will be arranged separately by the PLANES Qualitative research team and clinician directly following completion of the online questionnaire. This interview will be guided by the clinician interview topic guide (as detailed previously).

Clinician online questionnaire: As detailed previously, all clinicians who are eligible to take part in this WP will be sent an invitation email which will include information relating to why the study is taking place, why they have been invited to participate and what their participation will involve. This email will also contain a link to the online questionnaire for completion. When the questionnaire is complete a message will thank participants for their time.

7.2.1.5 Mixed Methods / Qualitative Analysis

Thematic analysis of qualitative data from the interviews, questionnaires and focus groups will be assisted using NVivo 10 qualitative data analysis package and SPSS software for statistical analysis. Whilst data will be analysed thematically the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (in particular, the design of the potential definitive RCT). Quantitative analysis will involve simple descriptive statistics and the chi-square test for trend. Data from each method will be analysed separately then synthesised through the use of constant comparative analysis.

7.2.2 Health Economic Outcome Measures

In line with the PLANES key objectives, the overarching aim of the economic analysis embedded in this study is to assess the feasibility of collecting relevant information on key economic outcomes. Such outcomes include health care resource use (e.g. care related to birth and complications, cost of additional diagnostic tests) and relevant structured quantitative outcomes, related to childbirth experience and maternal health-related quality of life. Childbirth experience will be captured through the use of the Childbirth Experience Questionnaire administered shortly after delivery [60, 61] . Quality

of life will be collected through the widely used EuroQol 5D-5L instrument, which will be administered before and after delivery [62]. The quality and completeness of the collected data will be assessed and findings will inform data collection methods and schedules in the subsequent RCT.

7.3 Sample Size

As detailed above no formal power calculation or primary outcome data will be determined. Success of the study will instead be determined on the acceptability of the study for women and clinicians. This will be determined by an ability to recruit and retain participants to the study. We propose that the study should expect to recruit in the region of 100 participants across two sites over a 12 month period. This is a pragmatic figure which is based on the typical number of SGA patients seen per annum in large consultant led NHS units within the UK.

7.4 Interim Analysis and Monitoring

As there are no formal hypotheses being tested, there are no formal stopping rules (other than safety) or mechanisms defined here to stop the study prior to the planned end of study. The study does have a formal oversight committee that will be able to review at regular intervals all accumulating data. The main responsibility of this committee will be to review the recruitment of participants, the collection of all essential data and to assess patient safety.

7.5 Statistical Methodology

Full details of the statistical analyses for this study will be detailed in the SAP. As the analysis being carried out are based on feasibility, the details in terms of the methodology may be altered during the course of the study. It will nonetheless be set out in the SAP and finalised prior to the final data lock and analyses. Some basic information to be followed are detailed here.

7.5.1 Patient Groups for Analyses

Patients will be summarised on an intention to treat basis retaining all patients irrespective of any protocol deviations. Further secondary analysis will be carried out on a per protocol population. Further analyses may be carried out on planned subgroups (e.g., those who meet the inclusion criteria for a future study) as is required.

7.5.2 Significance Levels

As this is an exploratory study no formal levels of significance are set. All statistics presented will be presented alongside 95% confidence intervals so as to give an indication of the level of precision only.

7.5.3 Missing Data

The likelihood of missing data are small given the standard procedure in place to manage the study centrally. Final analyses will take place on a complete-case basis with no adjustments made (e.g. multiple imputation) in the case of missing data.

7.5.4 Exposure to Intervention

The intervention will be a blood test only. Management will be determined in some participants (revealed sFlt-1/PlGF ratio) based upon the result of this blood test.

7.5.5 Trigger for Final Analyses

Analysis of study data will take place once all participants have received the planned follow-up and all data are available for analysis.

7.5.6 Data Descriptions

Continuous data will be summarised as median, inter-quartile range (IQR) and ranges. Categorical data shall be summarised as frequencies of counts and associated percentages.

7.5.7 Exploratory Analyses

Multivariate data analysis techniques will be used to attempt to find natural groupings in the generated data. In particular hierarchical cluster analysis (HCA) and principle component analysis (PCA) techniques will be used.

8. SAFETY

8.1 Introduction

The PLANES study **is not** a clinical trial of an investigational medicinal product. It therefore follows a study specific Safety Plan in line with Sponsor, REC and HRA guidelines.

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6 (R2).

8.2 Definitions

8.2.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence (i.e., any unfavourable or unintended sign including abnormal laboratory results, symptom or disease) in a research participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or

related to the intervention.

8.2.2 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward and unexpected medical occurrence or effect that

- results in death,
- is life threatening – refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe,
- requires hospitalisation or prolongation of existing inpatient hospitalisation,
- results in persistent or significant disability or incapacity, and
- is a congenital anomaly or birth defect.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

8.3 Notes on Adverse Event Inclusions and Exclusions

All Adverse Events for this study will be recorded at each study visit on the study eCRF. This study does not require the formal reporting of any non-serious AEs. The intervention to which participants are randomised to as part of this study provides additional care to that which is usually provided as part of local standard care. We therefore do not anticipate a large number of SAEs.

8.3.1 Include

The following AEs only should be reported for this study;

<u>Maternal AEs:</u>

- Preeclampsia
- HEELP
- Eclamptic fit
- Stroke
- Mechanical ventilation (not for caesarean)
- Myocardial infarction

<u>Neonatal AEs:</u>

- Hypoxic ischemic encephalopathy

- Retinopathy of prematurity
- Necrotising enterocolitis
- Bronchopulmonary dysplasia
- Respiratory distress syndrome
- Ventilated
- Cooling
- Seizure
- Confirmed bacterial infection
- Intraventricular haemorrhage

The following SAEs should be reported for this study;

- Fetal – Intrauterine death
- Maternal – Maternal death
- Neonatal – Neonatal death (up to age 28 days uncorrected)

Investigators must report all SAEs from randomisation to the end of the study. In addition, maternal death and maternal life-threatening complications, stillbirths and neonatal deaths are also pre-specified outcomes to be reported immediately as SAEs. All deaths reported as SAEs as part of this study will be reviewed regularly by a sub-committee of the ISDMC. The ISDMC charter will detail all information in relation to this review.

All SAEs must be reported within 24 hours of sites becoming aware of the event. Reporting should be completed by downloading the PLANES SAE form from the study portal, completing all fields on the form and then sending it to the Research Manager at the Harris Research Centre.
All SAE's will be subject to regular review by the oversight committees.

8.3.2 Do not Include

The following adverse events are anticipated in SGA pregnancies and therefore are exempt from immediate safety reporting (unless the investigator believes there to be a causal relationship to the study intervention).

- Maternal prolonged hospital stay (antenatal) related to the diagnosis of SGA or preeclampsia
- Maternal prolonged hospital stay (postnatal) related to the diagnosis of SGA or preeclampsia
- Termination of pregnancy (ToP; please note – fetal death associated with ToP should continue to be reported as an SAE, with ToP detailed in the notes)
- Hospital admission for

  - Any expected AE
  - Rest
  - Maternal discomfort
- Pregnancy induced hypertension
- Pre-eclampsia
- Threatened preterm labour (requiring tocolysis or steroids)
- Preterm delivery (in maternal interest)
- Preterm delivery (in fetal interest)
- Caesarean section
- Postpartum Haemorrhage (<500mls)
- Blood transfusion (maternal or fetal)
- Admission to neonatal intensive care
- Neonatal complications of prematurity

8.4 Notes on Grading of Adverse Events

The assignment of the severity / grading should be made by the investigator responsible for the care of the participant using the definitions below. Regardless of the classification of an AE as serious or not. Its severity must be assessed according to medical criteria alone using the following categories.

Table 3. Grading of Adverse Events

Grading	Criteria / Guidelines
Mild	*Does not interfere with routine activities (awareness of symptoms or signs, but easily tolerated [acceptable]).*
Moderate	*Interferes to some extent with routine activities (enough discomfort to interfere with usual activity [disturbing])*
Severe	*Impossible to perform routine activities (incapacity to work or to do usual activities [unacceptable])*
Life Threatening	*Results in risk of death, organ damage, or permanent disability (unacceptable)*
Death	*Results in death (unacceptable)*

A distinction is drawn between serious and severe AEs. Grading is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 8.2.2, hence, a severe AE need not necessarily be a Serious Adverse Event.

8.5 Relationship to Study Intervention

The assignment of the causality / relatedness should be made by the investigator responsible for the care of the participant using the definitions in Table 4 below. If any doubt about the causality / relatedness exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. In the case of discrepant views of causality between the investigator and other, the Sponsor, HRA and REC will be informed of both points of view within the regulatory reporting timeframes.

Table 4. Definition of Causality / Relatedness

Relationship	Description
None	*There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.*
Unlikely	*There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).*
Possibly	*There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the study intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).*
Probably	*There is evidence to suggest a causal relationship and the influence of other factors is unlikely.*
Highly Probable	*There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.*

8.6 Expectedness

An expectedness assessment using Reference Safety Information (RSI) and / or Investigators Brochure (IB) will not be completed for this study as it does not fall under the reporting requirement laid out in the Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031. Expectedness will therefore be assessed by the PI at site and the CI determining as to whether the SAE is in direct response to the study intervention.

8.7 Reporting

Any questions concerning adverse event reporting should be directed to the Research Manager in the first instance.

8.7.1 Non-Serious Adverse Events

All AEs should be reported on the study eCRF at the time of assessment (please see study schedule).

8.7.2 Serious Adverse Events

An SAE form should be completed and emailed / faxed to the Research Manager within 24 hours of becoming aware of the event.

8.7.3 Guidance on Reporting Serious Adverse Events

The PLANES SAE form can be downloaded from the study management portal within the REDCap CRF system. This should be completed by the Investigator at site. The Investigator should assess the SAE in terms of severity, causality / relatedness and expectedness. They should assess expectedness as to whether the SAE is in direct response to the study intervention (please refer to Section 8 and the PLANES Safety Plan for further guidance on completing these assessments).

In the absence of the PI, the SAE form should be completed by a designated member of the site clinical research team (as detailed on the site delegation log). The responsible individual should complete a final check of the SAE form, ensuring that all fields are complete and accurate – including no personal information relating to the study participant. Once this is confirmed, they should sign and date the form and forward to the PLANES Research Manager at the Harris Research Centre. Immediate reporting of SAE forms can be via:

1. email to the PLANES secure email account at PLANES@liverpool.ac.uk, or
2. Fax to PLANES Research Manager, PLANES Study Management Team, Harris Research Centre, Department of Women's and Children's Health, University of Liverpool **0151 795 9599**.

For urgent safety queries and where both fax and email systems have failed please contact the PLANES Research Manager on **0151 795 7320**.

An acknowledgement for all SAE reports will be sent to the site on the same day as the receipt of the report, where receipt is Monday – Friday, 9:00 – 17:00. For out of hours, weekends and bank holidays an acknowledgement will be sent by 11:00 on the next working day.

Please note – if no acknowledgement is received by the site within the timeframes set out here, they should contact the Harris Research Centre on 0151 795 7320 to confirm the SAE report has been received.

Following the completion of the SAE form and forwarding this to the Study Management team (as set out above); the PI must then notify their relevant R&D Department of the event, as per their standard local procedure.

In the event that an SAE requires follow-up, this should confirm that recovery is complete and the participant has returned to normal or stabilised. Follow-up information should be provided on the same PLANES SAE form (please refer to the PLANES Safety Plan for further guidance on the completion of the SAE form for follow-up). Additional supporting copies of test results can be provided separately.

The Investigator at site should ensure that the participant must be identified only by their unique study identification number and date of birth. The participants' personal information must not be included on any correspondence.

All investigators must ensure that multiple SAEs are reported separately on different forms - one report should be provided for each overall diagnosis.

Reports of related or unexpected SAEs should be submitted by the Research Manager within 15 days of the CI and Research Manager becoming aware of the event. This report should be completed on the REC SAE form for non-IMP studies.

8.7.4 Additional Reporting

All SAEs will be reported to Sponsor, REC and the HRA in line with regulatory requirements. Line listings will be provided to PIs and Sponsor on a three monthly basis; these will also be provided to the Study Oversight Committees. All SAEs will be reviewed as part of central monitoring by the Study Management Group (SMG).

8.7.5 Safety Plan

Prior to study green light approval, a PLANES Safety Plan will be put in place. This plan will contain further detail on how safety information will be processed, who is responsible for reporting and the timelines and methods for reporting. The PLANES Safety Plan will provide details of how safety information is triggered for review by the SMG, Oversight Committees and Sponsor.

9. REGULATORY ASPECTS

9.1 Medical Research Ethics Approval

The study will be conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

The study will be conducted in accordance with the EU Directive 2001/20/EC and the principles of Good Clinical Practice (GCP). Participants will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

This study may be terminated at the request of the CI, Study Oversight Committee, or REC if, during the course of the study, concerns about safety emerge.

9.2 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. Informed consent is required for all patients participating in University of Liverpool coordinated trials and studies. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate PIS and Consent form, describing in detail the study procedures and risks will be approved by an independent ethical committee and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. A contact point where further information about the study may be obtained will be provided.

After being given adequate time to consider the information, the participant will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient for their records, a copy will be placed in their medical records, and one further copy will be sent to the PLANES Research Manager by fax or secure email to PLANES@liverpool.ac.uk. The original should be retained in the Investigator Site File (ISF).

The participant may withdraw from the study at any time by revoking the informed consent. The rights and welfare of the participants will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

9.3 Study Discontinuation

If this study is prematurely discontinued (e.g., due to safety) all participants must be informed and the reason for the discontinuation should be written on the end of study form for each participant. If a participant has been withdrawn completely from the study whilst the study is still ongoing, an end of study form should be completed.

9.4 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. All eCRFs will be labelled with participants' unique study ID. Consent forms sent to the Harris Research Centre as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the study risk assessment. Such information will be stored in secure, locked cabinets and participants will be asked to explicitly consent to this transfer.

9.5 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol will be implemented within relevant institutions with responsibility for this study. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The study sites, facilities, laboratories and all data (including sources) and documentation must be available for audit and inspection by competent authorities or IEC. Such audits / inspections may take place at any site where study related activity is taking place (the Sponsor's site(s), the Harris Research Centre or at any investigator's site including laboratories).

The site staff should assist in all aspects of audit / inspection and be fully cognisant of the Sponsor communication strategy for single and multicentre studies. This includes management systems for the green light process prior to participant recruitment at site.

9.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6 (R2),

Guideline for Good Clinical Practice)) including the Investigator Study File, until the Sponsor or the Harris Research Centre informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic / practice or retires before the end of the required storage period. Delegation must be documented in writing. The Liverpool Clinical Trials Centre (LCTC) undertakes to store all electronic data related to completed eCRFs, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. At the point where it is decided that the study documentation is no longer required; the Investigator will be responsible for the destruction of all site study specific documentation and the Sponsor / LCTC / Harris Research Centre will be responsible for the destruction of all study related materials retained.

Verification of appropriate informed consent will be enabled by the provision of copies of participants signed informed consent forms being supplied to the Harris Research Centre by recruiting centres. This requires that name data will be transferred to the Harris Research Centre, which is explained in the PIS. The Harris Research Centre will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

9.7 Indemnity

This study is sponsored by the University of Liverpool and co-ordinated by the Harris Research Centre, Department of Women's and Children's Health within the University of Liverpool. The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical research study, including but not limited to the authorship of the study protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical study, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their

professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

9.8 Sponsor

The University of Liverpool will act as Sponsor for this study. It is recognised that as an employee of the University, the CI has been delegated specific duties, as detailed in the Sponsorship Approval letter and Internal Delegation of Responsibilities Agreement.

9.9 Funding

The National Institute of Health Research (NIHR) Research for Patient Benefit (RfPB) are funding this study. Study participants do not receive payments to take part in the main trial. Participants who take part in the qualitative work package of this study will receive payments for their travel as well as a gesture of goodwill.

A per patient payment has been calculated for this study. This has been approved by the Lead NHS Trust and North West Coast Clinical Research Network. All per patient payments will be set out in the study Research Site Agreement (RSA) where sites will also be provided with guidance on invoicing arrangements for processing payments.

9.10 Audits

The study may be subject to inspection and audit by the University of Liverpool under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017).

10. STUDY MANAGEMENT / OVERSIGHT

The day-to-day management of the study will be coordinated through the Harris Research Centre, Department of Women' and Children's Health.

10.1 Study Management Group (SMG)

An SMG will be formed comprising the CI, other lead investigators / core study management staff who are central to the day-to-day running of the study. The SMG will be responsible for the day-to-day running and management of the study and will meet at regular intervals throughout the course of the study. The frequency of meetings will be decided by the CI. However, it is expected that they should take place at least monthly. This group may consist of the following members of the core research

team however all are not required to attend each meeting in person. Compulsory attendance in denoted by a *.

- *CI
- *Research Manager
- Qualitative Work Package Representative
- Health Economics Work Package Representative
- Study Statistician
- Clinical Laboratory Representative

10.2 Study Oversight Committees

The PLANES study will convene both a Trial Steering Committee and an Independent Safety and Data Monitoring Committee. The details for which follow:

10.2.1 Trial Steering Committee (TSC)

The TSC will consist of

- CI / PI
- Independent Clinician (Chair)
- Research Manager
- Study Statistician
- One further Independent Clinician
- PPI Co Applicant
- Sponsor
- Lead Site Representative

The role of the TSC is to provide oversight of the study. In particular, this committee will concentrate on the progress of the study, adherence to the protocol, participant safety and consideration of new information. This committee must be in agreement with the final protocol and, throughout the study, will take responsibility for:

- Major decisions such as need to change the protocol for any reason,
- Monitoring and supervising the progress of the study,
- Reviewing relevant information from other sources, and
- Informing and advising the SMG on all aspects of the study.

In addition, this committee will convene to review individual participant data at regular time points throughout the recruitment period. In this way, they will review:

- Real time and cumulative safety data for evidence of study-related adverse events,
- Adherence to the protocol,
- Factors that could affect the study outcomes / compromise the study data, and
- Data relevant to informing the next stage of the study or a future study.

The TSC should conclude each meeting with a recommendation to the SMG as to whether the study pathway should be modified. This committee may convene at other time to assess any emerging safety data of other study related issues.

This committee will include experienced clinical researchers and other medical experts within the area. Meetings will be held (face to face or via teleconference) at regular intervals determined by need, but no less than once a year. The ultimate decision for the continuation of the study lies with this committee. Separate charters which will detail the committee terms of reference will be agreed at the first meeting which will detail how it will conduct business.

10.2.2 Independent Safety and Data Monitoring Committee (ISDMC)

The ISDMC will consist of the following independent members:

- Independent Chairman
- Independent Statistician
- Independent in the field of Obstetrics
- PLANES study Statistician

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, study conduct and external data. The ISDMC will first convene prior to study opening and will then define the frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in Section 7.4. The ISDMC will provide a recommendation to the TSC concerning the continuation of the study. A sub-committee of the ISDMC will meet as and when required to provide ongoing review on any maternal, fetal or neonatal deaths reported on the study as SAEs and to provide ongoing review of AE's. The remit for this will be detailed in the relevant committee charter which will be approved prior to overall study greenlight.

11. MONITORING

Central and study centre monitoring is conducted to ensure protection of participants in the study, and that procedures, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

A full quality control check of the protocol has been completed by the Harris Research Centre and the Chief Investigator. In addition, a SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) check has also been carried out in line with standard guidelines.

11.1 Risk Assessment

In accordance with the requirements of the Sponsor, a risk assessment has been completed in partnership with:

- Representatives of the Study Sponsors (University of Liverpool)
- Chief Investigator
- Members of the Study Management Group
- Research Manager
- Statistician

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur. The outcome of the risk assessment is categorised based upon the potential risk associated with the study intervention in accordance with MRC/DH/MHRA Project on Risk-adapted Approaches to the Management of Clinical Trials:

http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

- Type A: No higher than that of standard medical care
- Type B: Somewhat higher than that of standard medical care
- Type C: Markedly higher than that of standard medical care
- Non-CTIMP

The initial risk assessment for this study resulted in a study category of Low Risk. This is a non-CTIMP.

11.2 Source Data

Source data are all information, original records of 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 (original records or certified copies). (ICH E6 (R2), 1.51).

11.2.2 Source Documents

Original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical study. (ICH E6 (R2), 1.52)

For data where no prior record exists and which are recorded directly in the study workbooks (e.g., vital signs) the study workbooks will be considered the source document unless otherwise indicated by the investigator.

All data recorded in the workbooks should be consistent and verifiable with source data in source documents other than the workbook (e.g., medical record, laboratory reports and medical notes, scan reports). For this reason the study centre should maintain appropriate medical and research records for this study in compliance with ICH E6 (R2) GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of study participants for the purpose of source data verification.

11.3 Data Capture Methods

Study data will be captured using electronic case report forms (eCRFs) transcribed to a bespoke study database. This database is designed and maintained by the LCTC in collaboration with the Chief Investigator and Research Manager. The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded and all missing data explained.

11.3.1 Electronic Case Report Forms (eCRF)

All eCRFs are entered directly into the bespoke study database that can be accessed via a secure webpage by research site staff and the Research Manager. The client application is secured with a unique username / password combination allocated to each delegated member of the research team.

When data is entered into an eCRF it is electronically stamped with the date, time and the person who entered it. If data is changed on an eCRF, it is electronically stamped with the change and will be accompanied with the date, time, person and a reason for making the change or correction. The previous value is recorded in an audit trail for each data item.

Each eCRF contains specific validation checks on the data being entered. If any values are outside what is expected, or data are missing, this is flagged up and will be raised as a discrepancy on the main database system. Regular reports will be generated to identify discrepancies in the data, and allow for follow up. Comprehensive guidelines for eCRF data entry will be provided to all staff who have been delegated the responsibility for data collection. Where the site is unable to upload data using the eCRF a backup paper CRF will be available to use and accessed from the LCTC portal. In such cases the site research staff will enter the data onto the study database following the assessment.

Electronic and paper screening logs will be kept in clinics to record the number of patients declining participation and when volunteered the reason given. All data will be kept in a secure locked location on NHS premises. All routine eCRFs should be completed within a calendar month of the study visit occurring.

Paper workbooks will be available for download from the LCTC website http://www.lctc.org.uk. These will be used as an aid to research staff. To ensure current versions of the workbook are used, please print pages directly from the LCTC website as and when they are needed. Quality Control (QC) processes including on site source data verification will be put in place in line with the eCRF platform. Workbooks should be kept in the Investigator Site File at the research site.

11.4 Monitoring Methods

There are a number of monitoring features in place to ensure reliability and validity of the study data.

11.4.1 Green Light Process

The Green Light Process ensures that all regulatory and ethical approvals are in place, contracts / agreements are signed and study management standard operating procedures are in place prior to the study opening. Furthermore, a site greenlight process is will also be followed that ensures all study specific and ICH GCP training has been completed for site research staff before a study site is open and able to register participants. The green light process for opening this study will be managed by the Harris Research Centre.

11.4.2 Site Research Staff

All site research staff involved in the study must be included on the delegation log. The PI at each site signs off on the delegation log only those staff members he / she feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked (as part of the data management plan) against staff named on eCRFs, SAE reports and registration forms.

The Research Manager will ensure that as a minimum the PI, a research nurse, and a member of laboratory staff at site have study-specific training (on the protocol, SAE reporting and consent process) all of which is provided at site initiation (either on site or by teleconference) by the Research Manager and the CI. The PI is responsible for ensuring site staff named on the delegation log but not present at site initiation receive study-specific training (on the protocol, SAE reporting and consent process). Sites are provided with copies of training aids presented at site initiation to provide a constant reminder of key issues.

Delegated site research staff must also submit their CV and provide the date of their last ICH GCP training. In order to ensure that site research staff maintain up to date ICH GCP training (to be renewed every 3 years as agreed by the Sponsor). An automated email reminder is sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary NHS contracts and evidence of CRB checks must be obtained for staff (when necessary by UK law).

Email reminders (from site opening) will be sent to sites requesting that an updated delegation log is faxed to the Harris Research Centre. On receipt of updated delegation logs, the Research Manager will ensure that new staff members have submitted their CVs and date of last ICH GCP training.

11.4.3 Oversight

The PLANES study will have a Study Management Group, Trial Steering Committee and an Independent Safety and Data Monitoring Committee to monitor the study progress (see Section 10).

11.4.4 Safety Reports

Monthly safety reports will be generated by the Research Manager which allow monitoring of SAE reporting rates. Any concerns raised by the Oversight Committee or inconsistencies noted may prompt additional training, with the potential for the Research Manager to carry out site visits if there is suspicion of unreported SAEs in participant case notes. Additional training will also be provided if unacceptable

delay in safety reporting timelines (as outlined in the Safety Plan) is noted at a given site. AE's will be reviewed regularly by the oversight committees.

11.4.5 Eligibility and Consent

The Research Manager will verify that all site research staff attended study-specific training relating to eligibility screening and the informed consent / registration process. The Research Manager / delegate will carry out a check of all consent forms sent to the Harris Research Centre. This includes checking that the patient is eligible, the correct versions of the Participant Information Sheet (PIS) and Informed Consent (ICF) forms have been used and the patient and clinician signatures are present and dated on the same day.

11.4.6 Participant Confidentiality

All Study Management and site research staff have received ICH GCP training and are thus aware of the importance of patient confidentiality. The Research Manager / delegate will consistently check that all study documentation sent to the Harris Research Centre are anonymised and identifiable only by a unique study identification number (except for signed consent forms, which are stored in a separate locked cabinet in the Harris Research Centre). The Research i Manager / delegate will monitor site performance on maintaining patient confidentiality and will provide additional training if a particular site sends any patient identifiers to the Harris Research Centre (other than on the signed consent form).

11.4.7 Recruitment

The Research Manager / delegate will produce regular recruitment reports, to allow the Study Oversight Committees and Study Management Group to review recruitment. Slow or inconsistent recruitment will trigger further action centrally. The Research Manager / delegate may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. The Research / delegate will check that the study is being actively promoted at the research site, and site recruitment schedules will be reviewed during the course of the study as necessary.

11.4.8 Protocol Violations / Deviations

All protocol violations and deviations will be recorded by the Research Manager / delegate in the study site status database and are included in regular reports. The Research manager will send details of all protocol violations and deviations to the CI as soon as they have been made aware of them. The CI will then consider whether any are potential serious breaches that would need to be forwarded

immediately to the Sponsor. If it is noted that a particular site is making consistent protocol violations or deviations, additional training will be provided by the Research Manager.

11.4.9 Withdrawals / Losses to Follow-up and Missing Data

The Research Manager will produce reports on withdrawals, losses to follow-up and the quantity of missing eCRF data across sites for review by the Study Management Group and Study Oversight Committee. Identified problems will be discussed and remedial action taken as necessary.

As outlined in the data management plan, the Research Manager will check that the withdrawal eCRF is completed for all withdrawn participants (including the reasons for withdrawal). The Research Manager will compare withdrawal rates and reasons for withdrawal, paying particular attention to withdrawals close to dates of registration. If a site experiences an excessive rate of withdrawals, additional training on the informed consent procedure will be provided.

11.4.10 Data Management Plan

All eCRF data entered into the bespoke study database will be centrally monitored by the Harris Research Centre to ensure that data collected are consistent with adherence to the study protocol. The bespoke database used for this study includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised and emailed to site. A complete log of discrepancies and data amendments is automatically generated, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue.

Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in submitting eCRFs. This study will have a separate Data Management Plan which will detail all components of data management for this study.

11.4.11 Harris Research Centre Staff

All Harris Research Centre Study Management staff will receive regular ICH GCP training, have in-house training records and undergo regular individual Performance Development Review (PDR) sessions, all of which are used to ensure that appropriate training is received and any problems identified and resolved in a timely fashion.

11.4.12 Statistical Monitoring

Central statistical monitoring is carried out by the study statistician prior to providing each ISDMC report. The statistician checks randomisation numbers to ensure that there are none duplicated or missing, randomisation data, eligibility criteria and informed consent. Monitoring is used to highlight suspicions of fraudulent data (by carrying out range checks for unusual values, checking for consistency within participants and comparing data across sites to highlight inconsistencies). Safety and withdrawal data are also reviewed for completeness. If there is compelling evidence to suggest that data from a particular site may be fraudulent, the SMG may request a site visit to carry out source document verification of patient case notes and other source documentation.

11.5 Clinical Site Monitoring

11.5.1 Direct access to data

If necessary, a study monitor may need direct access to primary participant data, e.g. participant records, laboratory reports, appointment books, etc. Each PI therefore permits study related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data / documents. As this affects the participant's confidentiality, this fact is included on the Participant Information Sheet and Informed Consent Form.

11.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Case Report Forms will be labelled with participant unique study identification numbers. Consent forms sent to the Harris Research Centre as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the study risk assessment. Such information will be stored in secure, locked cabinets and participants will be asked to explicitly consent to this transfer.

11.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been / will be implemented within relevant institutions with responsibility for this study. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly. The study sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities or IEC. Such audits / inspections may take place

at any site where study related activity is taking place (the Sponsor's site(s), the Harris Research Centre or at any investigator's site including laboratories, etc.).

11.5.4 Records Retention

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Study File, until the Sponsor informs the investigator that the documents are no longer to be retained.
In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities).
The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.
The Harris Research Centre undertakes to store all data related to completed eCRFs, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. At the point where it is decided that the study documentation is no longer required; the Investigator will be responsible for the destruction of all site study specific documentation and the Sponsor/Harris Research Centre will be responsible for the destruction of all study related materials retained by the Sponsor.
Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the Centre for Women's Health Research by recruiting centres. This requires that name data will be transferred to the Harris Research Centre which is explained in the PIS. The Harris Research Centre will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

12. ARCHIVING

Data and all appropriate documentation should be stored for a minimum of 10 years after the completion of the study, including the follow-up period, unless otherwise directed by the funder / Sponsor / regulatory bodies.

13. PUBLICATION

The results of this study will be analysed and published once all study data has been collected, validated and analysed. Individual researchers must undertake not to submit any part of their individual data for publication without the prior consent of the SMG.

The SMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the study's CI(s), Statistician(s) and Research Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least.

The members of the Study Oversight Committees should be listed with their affiliations in the Acknowledgements / Appendix of the main publication. All publications arising from the PLANES Study will be open access, according to the conditions of the funder of the Study, NIHR RfPB.

14. PROTOCOL AMENDMENTS

All versions of this protocol prior to ethics submission are referred to as DRAFT.

Original Version	Original Date	New version	New date	Submitted to	Summary of Changes
DRAFT 2.0	**24-Oct-2018**	**n/a**	**n/a**	**Sponsor**	**None**
DRAFT 2.0	**24-Oct-2018**	**VERSION 1.0**	**19-Nov-2018**	**REC** **HRA**	**None**
VERSION 1.0	**19-Nov-2018**	**VERSION 1.1**	**05-Feb-2019**	**REC**	**Sponsor reference error amended (UoL003958 → UoL001423)**
VERSION 1.1	**05-Feb-2019**	**VERSION 2.0**	**06-Jan-2022**	**Sponsor** **REC** **HRA**	• **Update to the study duration to reflect the 21 month non-cost extension approved by the funder (NIHR RfPB)** • **Amendment to the inclusion criteria to include Normal Umbilical Artery Doppler** • **Amendment to the exclusion criteria to include severe maternal disease requiring urgent delivery** • **Increase to the volume of blood collected from participants per study visit (from 20ml to 25ml)** • **Revision to section 3.6) End of Study definition** • **Update to the contact details of the Sponsor Representative** • **Change to the Principal Investigator (PI) at the Liverpool Women's Hospital site** • **Minor document changes to the Participant Information Sheet (PIS) and Study Protocol** • **Amendment to section 8.3.3 – reportable AEs list updated**

VERSION 2.0	**06-Jan-2022**	**VERSION 3.0**	**03-Nov-2022**	**Sponsor** **REC** **HRA**	• **Amendment to St Mary's Hospital Laboratory contact (New contact - Alexandra Hasmi)** • **Amendment to Figure 1: PLANES study consort diagram** • **Amendment to participant management pathway:** - **Randomised Concealed: cCTG/USS as per local guideline, sFlt-1/PlGF Ratio and Research bloods at enrolment only** - **Randomised Revealed Normal Ratio: Research bloods at enrolment only, cCTG every 2 weeks** - **Randomised Revealed Abnormal Ratio: cCTG every week, no further sFlt-1/PlGF ratio or research bloods** - **Observational: Routine care, single sFlt-1/PlGF ratio at enrolment, offer delivery as per local clinical team** • **Inclusion of qualitative interviews for women (and partners) whose baby was small for gestational age in the womb within the last three years** • **Re-inclusion of section 11.5.4 Record Retention**

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