STUDY PROTOCOL

CRAFT: **C**erclage **a**fter **f**ull dilatation caesarean sec**t**ion;

an investigation into the role of previous in labour caesarean section in future preterm birth risk and potential management strategies

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Version and date of protocol amendments	2.0

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STUDY SYNOPSIS

Title of clinical trial	An investigation into the role of previous in labour caesarean section in future preterm birth risk and management strategies
Protocol Short Title/Acronym	**CRAFT**: **C**er**r**clage **a**fter **f**ull dilatation caesarean-sec**t**ion
Study Phase if not mentioned in title	Not applicable
Sponsor name	King's College London and Guy's and St Thomas' Hospital
Chief Investigator	Andrew Shennan, Department of Women and Children's Health, King's College London 0207188 3639 Andrew.shennan@kcl.ac.uk
REC number	19/LO/1270
Medical condition or disease under investigation	Increased risk of preterm birth following previous caesarean section in labour
Purpose of clinical trial	**CRAFT-OBS: Observational Study;** To evaluate subsequent pregnancy risk of preterm birth in women with a history of previous caesarean in established labour. This prospective study using clinically acquired cervical length and quantitative fetal fibronectin data will help establish a predictive model of preterm birth <34 weeks and <37 weeks. **CRAFT-RCT: Randomised controlled trial arm;** To assess treatment for short cervix in women at high risk of preterm birth following a caesarean section at fully dilated **CRAFT-IMG: Imaging sub-study;** To aid understanding of micro and macrostructural features within the cervix which predisposes to preterm birth in women with a previous full dilatation caesarean section. This will use MRI and an advanced transvaginal ultrasound protocol and to assess if structural changes can be visualised in the cervix.
Primary objective	1. **CRAFT-OBS**: To assess the risk of preterm birth or late miscarriage in women following an in labour caesarean section 2. **CRAFT-RCT**: To assess if cervical cerclage reduces preterm birth in pregnant women with a short cervix following a previous in labour caesarean section 3. **CRAFT-IMG**: To assess if alterations in MRI parameters or ultrasound characteristics occurs in women who undergo a late miscarriage or preterm birth following an in labour caesarean section.
Trial Design	Prospective observational study, nested randomised controlled trial and imaging sub-study in a selected cohort
Endpoints	Incidence of preterm birth at < 34 weeks gestation
Sample Size	CRAFT-OBS: 2200 women, CRAFT-RCT: 1000 women, CRAFT-IMP: 60 women

Summary of eligibility criteria	CRAFT-OBS: pregnant women 14^{+0}-23^{+6} week with a previous history of caesarean section in labour. CRAFT-RCT: pregnant women with a previous history of caesarean section carried out at full dilatation and a short cervix (≤25mm) in current pregnancy. CRAFT-IMG: pregnant women with a previous history of caesarean section carried out at full dilatation (30 women with cervix >25mm; 30 CRAFT-RCT participants).
Maximum duration of treatment of participant	Until delivery or removal of cerclage at 37 weeks gestation
Version and date of final protocol	Version 2.0 (10/09/19)
Version and date of protocol amendments	**To be inserted**

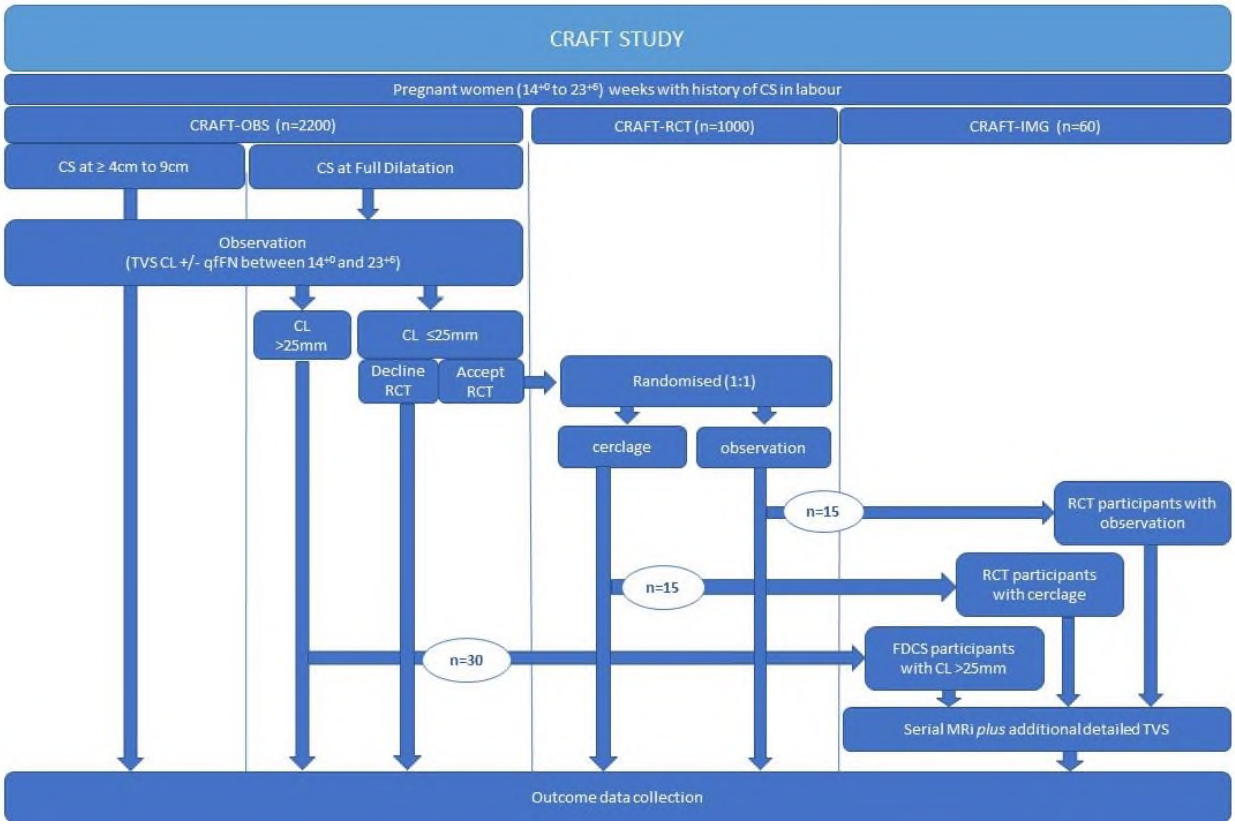

Figure 1: Flow of participants through CRAFT project

CRAFT

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LAY SUMMARY

Worldwide, there is a 9.6% rate of preterm birth before 37 weeks. The timing of preterm birth is directly related to the amount of risk to the infant at birth and for his/her long-term health. Very early preterm deliveries under 28 weeks gestation carry more risk for the development of the infant's lungs, risk of cerebral palsy, and eye problems just to name a few; not to mention the repercussions for parents supporting their infants in neonatal care at a detriment to the remaining family dynamics.

There are multiple factors which predispose women to preterm birth such as surgery to the neck of the womb, previous preterm birth and multiple pregnancies. A new factor now found to be contributing to this risk is if the mother has had a previous full dilatation caesarean section (FDCS) in labour particularly when she is 10cm dilated. We don't know how significant this risk is in the UK and the mechanism is not proven but what is known is that it particularly affects pregnancies under 28 weeks and also results in many late miscarriages (14-23^{+6} weeks). It is thought it occurs because a cut is made to the cervix (neck of the womb) at the time of the caesarean which weakens it. We do not routinely look for a scar on transvaginal ultrasound when measuring the cervical length (CL).

New NHS Commissioning guidelines(1) and *Saving Babies Lives Care Bundle*(2) has now recommended to screen all women with a previous FDCS because of this new widely reported risk. We don't know whether a cerclage (stitch) inserted into the cervix, first line prophylactic treatment in many UK units for a short cervix (≤25mm), works in this group of women. We have never imaged the cervix looking for injury in this FDCS group of women and compared it to our assessment with routine transvaginal ultrasound. We also do not know if a cut off of ≤25mm is a short cervix in women with a previous FDCS. Furthermore, we do not know how many women with a previous caesarean at 4-9cm dilatation has a risk of preterm birth in the future nor if our current tests of cervical length and fibronectin test work well to predict preterm birth in these women. A cerclage for a short cervix ≤25mm in women with a previous FDCS is not part of routine care. Hence why there is a three-pronged approach in CRAFT:

1. Observational study of women with a previous caesarean in labour
2. A randomised trial of women with a previous FDCS being treated with and without a cerclage if their cervix is short (≤25mm)
3. Imaging sub-study using transvaginal ultrasound and magnetic resonance imaging (MRI) to characterise any scars found to try to work out the mechanism of the problem.

PROFESSIONAL SUMMARY

Preterm birth (PTB), birth before 37 weeks gestation, has a global prevalence of 9.6% and over a million annual neonatal deaths. Recently, it has been observed FDCS are associated with recurrent, early premature births and late miscarriage (LM). Over 25% of all deliveries in the UK are by caesarean section (CS) and at least one in seven of these occur at full dilatation, affecting 20,000 women per year. These women have a six-fold increased incidence of subsequent preterm birth compared with women who undergo 1st stage CS earlier in labour, which equates to 2500 women per year in the UK. In women who lose a pregnancy, more than half will also go on to experience recurrent pregnancy losses in spite of current intervention. Prediction and management of these cases requires further understanding of its aetiology, assessment of current prediction strategies as well as clinical management.

Despite the emerging association between FDCS and the risk of PTB/LM, the risk following an in labour CS, not at full dilatation, is unknown. It is thought that late stage caesareans, from 7cm onwards, are likely to carry some risk of future preterm birth (3). Furthermore, our current predictive models of preterm birth based on transvaginal ultrasound and quantitative fetal fibronectin are not validated in this specific cohort of women. In this CRAFT study we will evaluate the risk of preterm birth in women with a previous history of caesarean section in labour.

Clinically, a short cervix (≤25mm) on transvaginal ultrasound scan (TVS) during the second trimester identifies women at high risk of PTB/LM. These women may benefit from prophylactic treatment such as a cervical cerclage but currently it is not part of routine care. At present it is unknown whether the ≤25mm cut-off is a reliable predictive measure of risk in women following in labour CS. The mechanism of late miscarriage and early premature births <34 weeks needs to be further understood with the imaging modalities available to us.

There will be three components to the CRAFT project: 1) CRAFT-OBS 2) CRAFT-RCT and 3) CRAFT-IMG Study

CRAFT-OBS: a study of risk and management in women with a history of CS in labour

We will screen all pregnant women with a history of caesarean section in labour booked for maternity care at all participating sites with transvaginal ultrasound and quantitative fetal fibronectin (if available) between 14^{+0} and 23^{+6} weeks with a previous in labour CS. These women will be grouped into:

1. Unknown dilatation at time of CS in labour.
2. Dilated 4cm to 9cm at time of CS in labour.
3. Full dilatation at time of CS in labour.

This part of the project will allow us to:

1. Determine pregnancy outcomes in women who have had previous in-labour CS.
2. Evaluate risk of PTB/LM according to degree of dilatation in previous in-labour CS.

3. Evaluate the predictive value of quantitative fetal fibronectin in women with previous CS in labour if done by direct care team for clinically indicated reasons at any point
4. Evaluate the predictive value of transvaginal ultrasound and whether cervical defects can be identified if performed by direct care team for clinically indicated reasons at any point.
5. Identify women who require referral into specialist preterm surveillance clinics.
6. Identify potential participants for CRAFT-RCT (see Figure 1).

CRAFT-RCT: a trial of USS indicated cerclage in women with history of FDCS

The aim of this trial is to evaluate efficacy of cervical cerclage in pregnant women with a short cervix (≤25mm) on TVS between 14^{+0} and 23^{+6} weeks gestation following a FDCS. The study will allow us to evaluate the impact of cervical cerclage on:

1. Primary obstetric outcome – spontaneous preterm birth rate <34 weeks gestation.
2. Secondary outcomes - Short-term pregnancy and neonatal outcomes, including a composite of neonatal death and morbidity.

CRAFT-IMG: a study evaluating imaging methods for assessing risk and management of women with a history of FDCS

This imaging sub-study will focus on analysis of TVS and magnetic resonance imaging (MRI) of cervical defects in this population to elucidate which women are at increased risk of PTB/LM. Assessment of any identified cervical defect and its relation to a cervical cerclage will also help us to establish which women at risk of PTB would benefit from this treatment.

Objectives of the imaging study:

1. To assess whether cervical abnormalities can be visualised in the cervix by TVS and MRi.
2. To determine which women in this FDCS cohort are most at risk of preterm birth.
3. To identify which women with a previous CS in established labour are most likely to benefit from a cervical cerclage.

Investigating the mechanism underpinning the increased risk of PTB/LM will aid our understanding of risk in women with a history of FDCS only and inform current and future treatment strategies. We will recruit 30 women with a CL of >25mm and 30 women with a CL of ≤25mm (short cervix). Women with a short cervix will be participants of the main RCT. Half of these women will have had a cervical cerclage as part of their management.

GLOSSARY OF TERMS

FDCS	Fully dilated caesarean section
CS	Caesarean section
MRI	Magnetic Resonance Imaging
PTB	Preterm Birth
LM	Late miscarriage
TAC	Transabdominal cerclage
CL	Cervical length
qfFN	Quantitative fetal fibronectin

1. Introduction

1.1. Background

Preterm birth (PTB), defined as birth less than 37^{+0} weeks gestation, is a significant health issue and is the most important single determinant of adverse infant outcome with regards to survival and quality of life(4). Morbidity is inversely correlated to gestational age, and the most significant adverse outcomes are associated with very preterm birth, defined as occurring less than 32^{+0} weeks gestation. Preventative measures which prolong fetal gestation by 1 week, such as those proposed by this study, could save health services £939 million per year in England and Wales(5).

The insertion of a suture around the cervix under regional anaesthesia is an established management strategy in those women at high risk of preterm birth. There is little consensus on the optimal procedure, technique or timing of insertion. Its mechanism of action has been hypothesised as not only supportive but as reinforcing the immunological barrier which protects the fetus from ascending vaginal infection. The benefit of an ultrasound indicated cerclage following evidence of cervical shortening (≤25mm) on transvaginal ultrasound scan has been reported to demonstrate a significant reduction in delivery <35 weeks gestation compared with expectant management (6).

The primary risk factor for PTB in multiparous women is a previous PTB(7). Emerging evidence has shown an association between late miscarriage (LM) (14-24 weeks) and PTB in women with a history of full dilatation caesarean section (FDCS) at term, affecting approximately 13.5% of these women. This is hypothesised to be due to a uterine incision, which is inadvertently too low, in or near to effaced cervical tissue. This occurs because the cervix becomes continuous with the lower segment of the uterus at full dilatation and the anatomy can often be distorted. Disruption and scarring of this cervical tissue is thought to result in cervical incompetence in future pregnancies. The association between FDCS and LM/PTB has only recently been recognised and it presents a pressing clinical problem.

Over 25% of all deliveries in the UK are by CS and up to 20% of in labour caesarean sections occur at full dilatation, which could affect up to 20,000 women in the UK per annum (8). These women have a six-fold increased incidence of subsequent preterm birth compared with women who undergo CS in the first stage of labour (adjusted odds ratio 5.8; 95% confidence interval 1.08-30.8)(3); 13.5% in comparison with 2%. This equates to around 2500 women per year in the UK. In women who lose a pregnancy, more than half will also go on to experience recurrent pregnancy losses in spite of intervention, compared to 14% of women with a history of preterm birth without previous FDCS (relative risk 3.06 95% confidence interval 1.22-7.71)(9). The relative risk of PTB in women with a previous emergency CS earlier in labour is unknown, however it is thought to be a continuum of risk, i.e. the later in labour the CS is carried out, the higher the risk of PTB in future pregnancies.

A screening programme to assess for cervical shortening in women with a previous FDCS is due to be implemented as part of new NHS commissioning guidance(1) and the revised *Saving Babies Lives Care Bundle*(2). It is unknown whether transvaginal cervical length screening for a short cervix predicts outcome in this group and there is currently limited evidence to inform optimal management of these women. It is also unknown whether first-line interventions for short cervix ≤25mm (vaginally-placed cerclages inserted in the distal cervix during pregnancy), used in other high-risk groups of women, is effective in this cohort. Preliminary data indicates that these interventions may be less efficacious, likely due to the injury having occurred in the proximal cervix, above the cerclage. A small retrospective analysis indicated that of 19 women who had experienced a LM/PTB subsequent to a FDCS and who then had a cerclage in the 3rd pregnancy, 10 (53%) still delivered <30 weeks gestation in comparison with 3% of a high-risk control group, who also had a cervical cerclage in situ after a LM/PTB (n=154).

This study has been developed in collaboration with the Preterm Birth Studies PPI Group at St Thomas' Hospital. They have confirmed that this issue is of vital importance to them and they will be consulted on all study literature and future directions associated with this project.

1.2. Rationale for study

The overall aim of the CRAFT project is to investigate the role of previous in labour caesarean section in future preterm birth risk and management strategies.

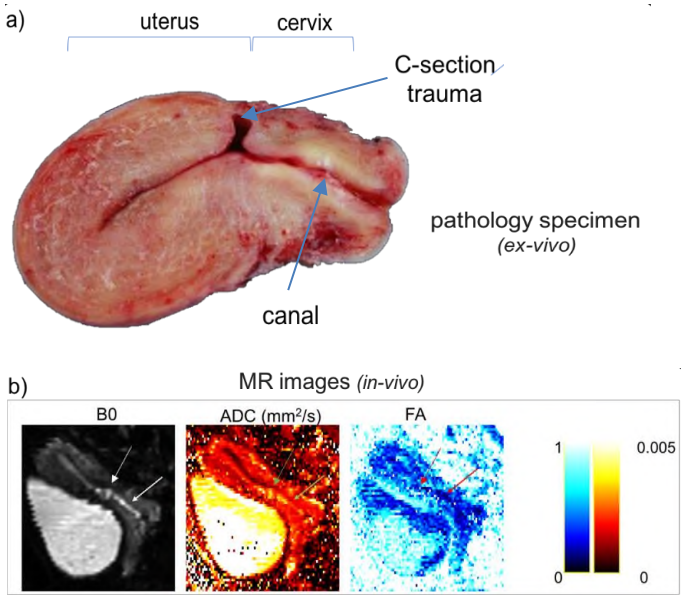
CRAFT-OBS will determine the risk of spontaneous PTB in women with previous CS in labour. We will use any data on qfFN testing and CL measurements to validate current predictive modelling of preterm birth using these tests, which are the most commonly used predictors of PTB. Participants whose CS was carried out at full dilatation, and whose cervix measures <25mm will also be invited to take part in the CRAFT-RCT (n=1000) and CRAFT-IMG (n=30). Participants with a history of FDCS and a cervix ≥25mm will be offered the opportunity to participate in CRAFT-IMG (n=30).

CRAFT-RCT will determine whether an ultrasound-indicated cervical cerclage is an effective management option in women with cervical shortening following a FDCS. It will also determine if a shortening cervix predicts outcome in this cohort. If it is demonstrated to be ineffective, further research will be required regarding alternative screening and treatment options. This may include imaging the cervix pre-pregnancy for evidence of cervical defects and/or offering a transabdominal cerclage (TAC) in the proximal cervix pre-pregnancy above the level of hypothesised defects.

CRAFT-IMG will inform development of methods for identifying cervical defects in women with a history of CS in labour. We will explore the value of scanning the cervix for scars/areas of abnormality to indicate which women are most at risk of adverse outcomes and require further monitoring and therapy. Currently the ultrasound-assessed CL is the only parameter used in

clinical practice to guide management of women at high risk of PTB and this has not been validated in women with previous FDCS. There is a need to evaluate the features of the cervix and any scar tissue by both MRI and US to evaluate which characteristics can accurately determine which women are likely to go on to experience LM/PTB. Preliminary data indicates that scars can be consistently identified on ultrasound and their location defined in relation to the internal-os of the cervix. MRI can provide additional information regarding tissue microstructure. Previous studies have indicated that changes in signal intensity of cervical stromal layers have been found on T2 weighted images(10) and alterations in basic diffusion imaging (a measure of Brownian motion of water molecules in tissue enabling assessment of microstructure) with relation to the onset of labour reported(11). This will help evaluate the value of imaging and our ability to predict who will need a cerclage – for example location of scar from FDCS.

The development of sophisticated diffusion techniques such as Intravoxel Incoherent Motion (IVIM), has enabled assessment of tissue microstructure, diffusivity and perfusion(12). This separates diffusion perfusion from true diffusion effects, the signal decay is described by a biexponential instead of a mon-exponential equation which yields a more accurate description of the underlying tissue properties(13). This technique has been used to assess perfusion in cervical carcinoma(14) but has not been investigated in relation to PTB. Professor Daniel Alexander (UCL), a world leading expert in the field of diffusion MR imaging, has previously harnessed these techniques in the assessment of the breast, brain, placenta, and prostate. In this project, his team will facilitate optimal data acquisition and analysis of the cervix using IVIM.



Pilot Data

Figure 1: *preliminary data demonstrating the basic quantification of cervix microstructure with MRI. A cervical defect can be seen ex-vivo from a pathology specimen of a uterus and cervix where the patient had previously undergone a full dilatation caesarean section (a). MRI imaging shows a similar cervical defect (b). The left image is T2 weighted and apparent diffusion co-efficient (ADC) map and fractional anisotropy (FA) maps, both reflecting tissue structure can be seen in the centre and right images. The cervical defect is indicated with the left arrows. The right arrows indicate the cervical canal.*

Defects in the cervix have already been identified by our research group in non-pregnant women who have undergone LM/PTB following a FDCS using MRI. These lesions are comparable to pathology specimens of women with a similar history (see Figure 1).

Ultrasound is a commonly used modality in obstetrics to quantify the CL. The CS scar can be easily identified in the lower uterine segment or cervical tissue using transvaginal ultrasound examination. Using Doppler ultrasound the internal os is identified relative to the height of the uterine arteries bilaterally as they traverse lateral to the cervix (methodology developed by Professor Anna David at University College London Hospitals). The scar defect position has been studied prospectively in women with a previous FDCS who booked at University College London Hospital. Results in 87 women seen over 14 months found a 37% rate of PTB in 8 women whose scar defect was ≥5mm from the internal os or within the cervix itself, compared to 5% of 21 women whose scar defect was >5mm above the internal os. We will use the same methodology in this trial and imaging study. We will also analyse inter/intra-observer variation in performing cervical ultrasound assessment and compare it to MRI images.

2. Study aims and objectives

2.1. Aims

There are three overall aims of the CRAFT project which correspond to each distinct part:

i. To understand the association between the degree of cervical dilatation at CS in labour with risk of LM/PTB in subsequent pregnancies.
ii. To assess the efficacy of cervical cerclage for a short cervix ≤25mm detected by transvaginal ultrasound in a randomised controlled trial of women with previous FDCS (CRAFT-RCT).
iii. To identify a mechanism for the increased risk of preterm birth with MRI and transvaginal ultrasound in order to predict those at most risk and whether cervical cerclage would be of benefit (CRAFT-IMG)

2.2. Study objectives

2.2.1. CRAFT-OBS: a study of risk and management in women with a history of CS in labour

i. Determine the incidence of LM and PTB (prior to 37 weeks) in women with previous CS in labour stratified by cervical dilatation.

ii. If ultrasound measured cervical length and quantitative fibronectin are carried out, this data will be collated and help evaluate the ability of these tests to determine risk of preterm birth in women with a history of in labour caesarean.

2.2.2. CRAFT-RCT: a trial of USS indicated cerclage in women with history of FDCS

i. Determine if an ultrasound-indicated cervical cerclage is effective management in women with a history of FDCS and cervical shortening (<25 mm) in preventing LM or PTB <34 weeks gestation. Evaluate the impact of intervention on short-term fetal and neonatal outcomes, assessed as a composite of fetal and perinatal death and major morbidity.
ii. Assess the impact of both management strategies (i.e. cerclage and observation) on health economic outcomes for mother and infant in terms of number of nights in hospital; cost data to hospital discharge/28 days post delivery.

2.2.3. CRAFT-IMG: a sub-study evaluating imaging methods for assessing risk and management of women with a history of FDCS

i. Ascertain whether MRI or ultrasound (or a combination of the two) can accurately predict PTB when abnormalities are detected in the cervix.
ii. Identify which women are most likely to benefit from intervention.

3. Study Design

3.1. CRAFT-OBS

This is a multicentre prospective cohort observational study of 2200 pregnant women with a previous history of CS in labour who will be recruited following their booking or scanning visit (Appendix: participating sites). Women who have had a previous FDCS and who are found to have a CL ≤25mm on transvaginal ultrasound will be offered recruitment to the CRAFT-RCT (see below). Women with a previous FDCS and a CL ≥ 25mm may be invited to participate in CRAFT-IMG. If patients have a clinically indicated transvaginal cervical length or qfFN during their pregnancy, this information will also be collected.

3.2. CRAFT-RCT

This is a multicentre randomised controlled trial (RCT), carried out over 27 months in at least 41 hospitals performing surveillance (n=1000). All women with a history of FDCS will have CL

monitoring as per new guidance <24 weeks(1). If their cervical length is or becomes <25 mm they will be randomised (1:1) into one of two groups:

- cervical cerclage plus standard management
- standard management

3.3. CRAFT-IMG

This is a prospective cohort sub-study collecting image data and outcomes in a sub-group of women participating in CRAFT-OBS (n=30) and CRAFT-RCT (n=30).

The subgroup will be recruited from participants attending University College London and St Thomas' Hospital only. All participants will have experienced FDCS in a previous pregnancy and will include women with and without cervical shortening in the current pregnancy based on their CL monitoring. Participants will be allocated to one of three groups: a) women with cervical length of <25 mm who have been randomised to cerclage in CRAFT-RCT (n=15), b) women with cervical length of <25 mm who have been randomised to observation in CRAFT-RCT (n=15), c) women with cervical length of ≥25 mm.

A transvaginal ultrasound using a new enhanced protocol developed by Professor Anna David at UCL will be undertaken in all women. This procedure is more detailed than standard measurement of CL. The site of previous scar tissue and any other abnormalities (for example the presence of cysts) will be recorded. Serial MRIs will also be performed. Recruited patients will have up to 3 serial transvaginal ultrasounds and MRIs during their pregnancy.

3.4. Expected study duration

Recruitment will be conducted over a 24 month period. The end of the study will be defined as 28 days post-delivery or discharge from hospital (whichever sooner) of the last recruited participant and infant. Women will be followed-up until postnatal discharge. The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely.

4. Study Endpoints

4.1. CRAFT-OBS

Primary endpoint:

i) Delivery < 37 completed weeks gestation (powered).

Secondary endpoints

i) Adverse perinatal outcome, defined as a composite outcome of death (antepartum/intrapartum stillbirths plus neonatal deaths prior to discharge from neonatal services)
ii) Delivery <34 weeks gestation.
iii) Gestation at delivery.
iv) Late miscarriage (14^{+0}-23^{+6} weeks).
v) Healthcare use, e.g. appointments, hospital admission, cervical length, cervicovaginal fetal fibronectin levels, interventions.
vi) Predictive modelling to evaluate the ability of CL and fFN to determine risk of preterm birth <34 and <37 weeks
vii) Other maternal and fetal morbidities, as per COPOP core outcome set for preterm birth intervention studies(15).

4.2. CRAFT-RCT

Primary endpoint:

i. Delivery <34 weeks gestation (powered)

Secondary endpoints:

i. Adverse perinatal outcome, defined as composite outcome of death (antepartum/intrapartum stillbirths plus neonatal deaths prior to discharge from neonatal services) or one/more of intraventricular haemorrhage, periventricular leukomalacia, hypoxic ischaemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia and sepsis.
ii. Gestation at delivery.
iii. Requirement for rescue cerclage (bulging fetal membranes).
iv. Time between intervention and delivery.
v. Health costs at 28 days post-delivery.

4.3. CRAFT-IMG

Primary endpoint:

i. Alterations in imaging parameters between women with a full dilatation C-section in a previous pregnancy and either a cervix ≤25mm or a cervix >25mm in this pregnancy which culminates in a preterm (<37 week) delivery.

5. Sample size and power calculation

All power calculations were performed by the trial statistician Paul Seed.

CRAFT-OBS: With estimated prevalence of 15% preterm birth rate prior to 37 weeks, and 16.2% of all deliveries being by emergency caesarean section; we will require data on 2200 women to estimate the event rate to 10% relative accuracy (e.g. 13.5% to 15.6%).

An average district general hospital has 4,000 deliveries per year, of which 648 (16.2%) might be by Emergency Caesarean. We aim to recruit 324 of these (50%) at a minimum of 7 study sites. At St Thomas' Hospital rather fewer deliveries (11%) are caesareans in labour; so we will aim for at least 20 sites, taking the assumptions above into account.

If we acquire data of cervical length and/or quantitative fetal fibronectin in this cohort, we will be able to validate these prediction tools. If we treat a short cervix of ≤25mm, and a raised qfFN of >=50ng/ml as positive tests, we anticipate a 75% sensitivity and 83% specificity from the literature for both tests (16).

Assuming 10% event rate, 1000 women (100 cases and 900 controls) would allow use to estimate the sensitivities of qfFN and CL to within 10% and the specificities to within 3% of the true value. The PPV would be estimated within 7% and NPV within 1.5% of their true values.

CRAFT-RCT: Pilot data indicates that at least 10% of all births and 70% of preterm births associated with FDCS occur before 34 weeks. In order to detect a reduction in this rate from 10% to 5% 474 women are required in each group to give 80% power. We will aim to recruit 500 in each arm in order to allow for 5% loss to follow-up.

CRAFT-IMG: We consider that the participation of 60 women in this sub-study will provide useful information for planning future research; this is achievable by recruiting at 2 sites (UCLH and St Thomas' Hospital): 30 women with cervix >25mm and 30 women with cervix ≤25mm (15 women with cerclage, 15 women without).

If we have data from participants in this study of their cervical length and/or quantitative fetal fibronectin we will be able to carry out predictive statistics. This would involve calculating ROC curves for prediction of spontaneous preterm birth for both fibronectin and transvaginal cervical

length measurement as a continuous variable, for delivery <24, <30, <34 and <37 weeks gestation. From the optimal thresholds, predictive statistics will be calculated.

6. Participant inclusion and exclusion criteria

6.1. Inclusion and exclusion criteria for ALL CRAFT participants

Inclusion criteria:

- Pregnant women under 23^{+6} weeks gestation with a history of previous caesarean section in labour.
- Singleton pregnancy.
- Willing and able to give informed consent (with or without interpreter).

Exclusion criteria:

- Under 16 years of age.
- Inability to give informed consent.
- Previous caesarean section carried out before labour.
- Women who have been commenced on management with progesterone, a cerclage or arabin pessary as part of their care or another research study

6.2. Inclusion and exclusion criteria specific to CRAFT-RCT

Inclusion criteria:

- Pregnant women between 14^{+0} and 23^{+6} weeks gestation with a history of FDCS.
- Short cervix (≤25mm) on transvaginal ultrasound scan.

Exclusion criteria:

- Women with persistent fresh vaginal bleeding evident on speculum examination.
- Women with visible fetal membranes evident on speculum examination or open cervix on ultrasound scan.
- Women with severe abdominal pain/evidence of sepsis (as judged by attending clinician).
- Known significant congenital or structural or chromosomal fetal abnormality.
- Suspected or proven rupture of the fetal membranes at the time of recruitment.

6.3. Inclusion and exclusion criteria specific to CRAFT-IMG

Inclusion criteria:

- Pregnant women between 14^{+0} and 23^{+6} weeks gestation with a history of FDCS.

Exclusion criteria:

- Contraindications to MRI, e.g. claustrophobia, BMI >40 kg/m2 (due to technical limitations of scanner) or a women with a non-MRI compatible metallic implant.

7. Study procedures

7.1. Identification of participants

CRAFT-OBS

We will recruit pregnant women who are booked for their delivery at participating centres who provide written informed consent to participate in the study and who meet the study eligibility criteria.

Women who have previously had an emergency caesarean in labour will be identified through their booking appointment or scan appointments by the direct care midwife, doctor, sonographer and approached with information about this observational study. Clinical midwives, doctors or sonographers will highlight eligible women to the research team. The research team will then be able to discuss the research with patients if they are eligible at the time of their first trimester or second trimester scan.

CRAFT-RCT

Women participating in CRAFT-OBS will be eligible for CRAFT-RCT if they are found to have a cervix ≤25mm prior to 23^{+6} weeks gestation with a history of FDCS. Women with a previous full dilatation caesarean section will be identified by a member of the direct care team and referred for cervical surveillance as per new guidance (1,2). The research team will check relevant hospital records when patients are consented in order to confirm a previous full dilatation caesarean section occurred. If these records are not available for review the patients will be excluded. Eligible women will be informed about the trial by a doctor, sonographer or midwife if their transvaginal ultrasound confirms a short cervix (≤25mm). Members of the research team

(midwives, doctors and scanning practitioners) can then discuss the research further and consent women.

- If a woman is randomised to a cervical cerclage, the procedure needs to take place within 7 days of diagnosis of cervical shortening and removed around 37 weeks gestation. She will also have regular scan surveillance in accordance with local protocols. Rescue cerclage can be offered in cases of cervical opening with exposed membranes as per local guidelines. Targeted admission for bedrest and steroids can also be offered as per clinician practice and local protocols.

- If a woman is randomised to the standard care arm; she will have regular surveillance scans and clinic visits in accordance with local protocols and clinician practice. Rescue cerclage can be offered in cases of cervical opening with exposed membranes as per local guidelines. Targeted admission for bedrest and steroids can also be offered as per clinician experience and local protocols.

Concomitant medication during RCT

Participants are permitted to use any concomitant medication or treatment except progesterone alongside the trial management. This will be recorded at every visit on the RedCap database. Any other medication or treatment that would form normal clinical management for these women at risk of preterm labour i.e. antibiotics, corticosteroids, tocolytics etc. will be permitted according the local hospital guidelines and clinician preference.

CRAFT-IMG

Participants will be identified from CRAFT-OBS (30 women with history of FDCS and cervical length >25mm) and CRAFT-RCT (30 women with FDCS and short cervix (≤ 25mm) by their direct care team. Interested women will be directed to have more information from the research team as well as confirmation of informed consent. 15 women from CRAFT-RCT will have been randomised to cerclage and the other 15 to standard management. Only women recruited at St Thomas' Hospital and UCLH will be eligible for this part of the CRAFT project. Doctors, sonographers or midwives in the research team will be recruiting patients to this sub-study.

All MRI scans will be performed at St Thomas' Hospital, and advanced protocol transvaginal ultrasound scans will be performed at both UCLH and St Thomas' Hospital. Repeat imaging will

be undertaken at regular intervals up to a maximum of 3 MRIs and 3 TVUS depending on patient availability in order to assess changes in the cervical tissue using the two imaging modalities.

7.2. Consent procedure

The study will be verbally explained to potential participants who will be given a written patient information sheet and adequate time for consideration and clarification of any queries. They can take the information home. For CRAFT-OBS and CRAFT-IMG, eligible patients will have until their next appointment to decide on participation and provide informed written consent. For CRAFT-RCT, eligible patients will generally have up to 48 hours to decide on participation, depending on the length of their cervix and urgency of treatment as determined by the attending clinician.

Written consent will be confirmed by an appropriately trained (GCP) clinician or researcher. Three copies of the consent form will be taken (1 for participant, 1 for clinical notes (unless electronic records), 1 for site file). At the time of recruitment, a unique study number will be allocated to the patient. Only one copy of patient identifiable data linked to this number will be recorded on a password protected KCL computer in order that recruits can be contacted and delivery outcomes recorded. The research record will contain minimal identifiers such as initials and date of birth. Keeping initials and date of birth on the research database allows the data to be double-checked against source outcome data, therefore enhancing the reliability of the data.

Consent will be sought to obtain NHS numbers for future tracking of outcomes. NHS numbers (mother and baby) will be collected to aid linkage to these future health records as well as follow up pregnancy and neonatal outcomes for recruits who move away from study sites. NHS numbers will be held separately from main study data and only linked with study ID. Access to this information will be limited to specific study staff. They will also be explicitly consented for use of the study data for future research, collection of additional data on any future pregnancies and whether they would be happy to be contacted about participation in further research studies that may be of interest to them.

7.3. Data Collection

Following consent, data on the participant's demographic characteristics, risk factors, medical and obstetric history will be documented and entered onto the study specific database. This will include current and previous monitoring procedures and/or pregnancy interventions (e.g. cervical length measurements and cerclage). Cervical length will be measured with transvaginal

ultrasound in accordance with local protocols, measurements will be taken in triplicate and the shortest measurement used. Their pregnancy and neonatal outcomes will be collected from NHS patient records postnatally.

Participants with a history of FDCS will be referred to a preterm surveillance clinic where they will be invited for cervical length assessment (with or without other tests, such as fetal fibronectin) from 14+0 to 23+6 weeks gestation. Cervical length will be measured with transvaginal ultrasound in accordance with local protocols, measurements will be taken in triplicate and the shortest measurement used. If their cervical length is, or becomes ≤25mm during this period they will be offered the opportunity to participate in CRAFT-RCT. Further explanation and a separate information sheet will be provided and additional consent form will be completed and stored as those for the main study. If the participant is unwilling to participate in this randomised controlled trial she will continue to be monitored and cared for as per local protocol/clinicians' experience, and continue in the observation arm of CRAFT study. Outcome data will be collected after the birth of her baby. Women who provide written informed consent will be randomised to either cervical cerclage or standard care.

Sixty participants, recruited at St Thomas' and UCLH, will be invited to have additional imaging tests for the sub-study, CRAFT-IMG. They will be given additional information and asked to sign another consent form, which will be stored as described above. These additional tests will involve serial transvaginal ultrasound measurements of cervical length and macro/microstructural changes as per Prof Anna David's protocol and MRI scans of macro/microstructural cervical change.

Serial MRI scans will be performed on a 3-Tesla MRI scanner at St Thomas' Hospital. Conventional imaging will include high resolution T1 and T2 weighted images as well as diffusion datasets. The first advanced protocol transvaginal ultrasound and MRI will occur at any time from 20 weeks gestation. Where delivery has not occurred, further imaging will be offered (up to a maximum of 3 MRI and 3 of these transvaginal ultrasound scans).

Outcome data: All participants' data will be collated up until postnatal discharge. Neonates will be followed up until discharge or 28 days (whichever is sooner). Prompts on the database will alert the research midwife/assistant when each trial participant reaches her delivery date. Birth registers and in-patient records will be used to track hospital admissions and pregnancy outcomes. Outcome data (medical and economic) will be collected by review of NHS Maternity and medical records. If information is unavailable, e.g. if the delivery occurred elsewhere, the patient, patient's GP or other hospital will be contacted. Gestational age will be calculated using

ultrasound estimated date of delivery predicted at the 12-15 week ultrasound scan. The primary and secondary outcome data will be collected from hospital records after discharge from neonatal care.

Source data and documents will be accessible by the research team only and any paper records will be stored in a locked cabinet in the Principal Investigators' offices. Electronic versions of these source documents are stored on Trust computers only and behind the NHS firewall. The study may be subject to inspection and audit by King's College London and Guy's and St Thomas' NHS Foundation Trust under their remit as sponsor and co-sponsor respectively, and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care.

The identifiable information obtained as part of this study will be managed in accordance with the General Data Protection Act (2018). The computerised information is protected by a software and hardware barrier, and the records are handled in the same way as hospital records. Data will be stored for 25 years in Trust firewalls/KCL Firewalls in accordance with legal requirements for the storage of maternity records.

7.4. Trial intervention and additional imaging (CRAFT-RCT and CRAFT-IMG)

At time of recruitment for CRAFT-RCT women will be randomly assigned (1:1) to cerclage or surveillance. Randomisation will be carried out online via the RedCap web platform. Users will be assigned a personal identifier number. Due to the nature of the interventions, the study is not blinded to the care providers or patient. Recruiters and trial co-ordinators will not have access to the randomisation sequence. Women will be informed at time of recruitment to which arm they have been randomised. A 'minimisation' procedure, using a computer-based algorithm, will be used to avoid chance imbalances in important stratification variables. Stratification variables will be a) gestation, b) BMI <30 or ≥30 kg/m2 c) risk factor (previous premature delivery <24 weeks, PPROM, late miscarriage or previous cervical surgery). Women will not know what treatment they will be allocated prior to recruitment. RedCap will write the randomisation program and hold the allocation code. Contact information will be obtained from the patient. Demographic measures such as ethnicity, BMI etc will be entered into the central trial database.

Following randomisation in CRAFT-RCT, the attending clinician will arrange for either a cervical cerclage (to be carried out within 7 days) or further observation as the randomisation indicates.

There is no "emergency code break" procedure as the trial is open label randomised trial. The method and materials used will be according to local protocols and clinician preference.

Indications for withdrawal of treatment (removal of cerclage):

- Participant request.
- Elective preterm delivery.
- Fetal membrane rupture.
- Symptomatic placenta praevia.
- Completion to 37 weeks gestation.

Indication for additional treatment (rescue/emergency cerclage):

- Exposed membranes or open cervix at 16^{+0}-27^{+6} weeks gestation.

The final study visit will take place between 34+0 and 37+0 weeks gestation. For those in the cervical cerclage arm an appointment for removal will be made for 37 weeks as per local policies and practice. If delivery occurs prior to this time the research team will collect this outcome data. Apart from the final study visit (34+0 and 37+0 weeks), all trial visits will occur during routine clinic attendances according to local clinical protocols and clinician practice.

Participants of the imaging sub-study (CRAFT-IMG) will have a minimum of 1 advanced transvaginal ultrasound and 1 MRI up to a maximum of 3 MRIs and 3 advanced protocol transvaginal ultrasound scans (around 5 minutes longer than a cervical surveillance transvaginal ultrasound). The number carried out depends on the length of the pregnancy and patient's availability. Where possible these will be co-ordinated with clinical appointments to minimise disruption. Participants will be offered reasonable reimbursement for their travel for these additional appointments.

8. Data analysis

CRAFT-OBS: This study will calculate prediction of preterm birth <37 weeks gestation in women with a previous CS in labour by observing clinical pregnancy outcomes. Where data is available the predictive value based on cervical length and quantitative fetal fibronectin will also be assessed. Results will be presented as both odds ratios and risk differences. Standard predictive statistics will be used for prediction of delivery <34 and <37 weeks gestation.

CRAFT-RCT: CRAFT-RCT: Statistical analysis of results will be undertaken by the research team and Mr Paul Seed. The primary analyses will be by intention to treat. The main outcome is delivery under 34 weeks. Secondary analyses will include secondary endpoints as per section 4.2. Standard predictive statistics will be used for prediction of delivery <34 weeks gestation (cervix ≤25mm will be calculated along with area under the curve). We will also validate our current predictive tools of cervical length and fetal fibronectin in this population. Results will be presented as both odds ratios and risk differences, leading to number needed to treat (NNT) if appropriate, according to CONSORT guidelines. A subgroup analysis will be carried out according to other risk factors for preterm birth other than FDCS.

CRAFT-IMG: This sub-study will provide data on relationships between macro/ micro-structural cervical defects in pregnant women who have had a previous FDCS and a short cervix ≤25mm, compared with those who have a cervix >25mm. Comparison will be made between the two groups. Relative efficiency of detection of cervical defects by MRI (and relationships with outcomes), will be compared to those identified by ultrasound. We will also assess changes in the cervix over time. This will be performed in conjunction with senior statistician Mr Seed. Images will be assessed for: overt structural abnormalities in collaboration with radiologists using a structured proforma. Patients and clinicians will be informed of clinically significant findings. These images will be compared to TVUS images in order to ascertain whether there is any correlation in findings between the two modalities (ref 910).

Ultrasound data will be analysed contemporaneously at acquisition. MRI data will be assessed for cervical anatomical features and presence and location of overt lesions or disruptions on conventional imaging (blinded to the participant's history). Models will be fitted using the open-source toolkits for diffusion data by Dr Hutter and Dr Paddy Slator (UCL)[10,11], to obtain quantitative maps of tissue composition and microstructure properties. We will analyse the different imaging findings between short and long cervices and correlate it with their perinatal outcomes.

9. Study Governance

9.1. Ethics & Regulatory Approvals

The study will comply with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework. This protocol and related documents

will be submitted for review and receive approval from the Research Ethics Committee (REC). Additionally, local R and D approval will be sought in all participating centres. Any future amendments, progress and final reports will be submitted as required. The study and any amendments will only be implemented following Ethics Committee and Trust approval by the R&D Department in each participating centre.

9.2. Assessment of Efficacy for MRI and transvaginal ultrasound

Image quality will be assessed by the research team.

9.3. Procedures for Assessing Efficacy Parameters

The within the research programme. Image quality is reviewed weekly and persisting issues analysed and appropriate action taken. This occasionally involves calling scanner engineers to fix a fault.

9.4. Specification, Timing and Recording of Safety Parameters

CRAFT-IMG: Each woman is assessed prior to MRI examination to ensure there are no contraindications to scanning. This includes a health check and a detailed metal safety check. Women are carefully placed inside the scanner to ensure comfort and safety. We are also in constant contact with the woman during the examination so if she is uncomfortable or feels unwell we can remedy the situation immediately. Full resuscitation equipment is always available outside the scanner and staff are trained in basic life support. Any adverse events are recorded as for any Trust patient.

9.5. Safety

9.5.1 Assessment of Safety

The Data Monitoring Committee (DMC) will be convened to ensure the wellbeing of study participants and the quality of the data collected (see below section 9.8). The committee will periodically review study progress and outcomes as well as reports of serious adverse events (SAEs). The DMC will, if appropriate, make recommendations regarding the continuance of the study or modification of the study protocol.

9.5.2 Procedures for Recording and Reporting Adverse Events

Serious adverse Event (SAE), Serious Adverse Reaction (SAR)

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious adverse Event (SAE) or Serious Adverse Reaction (SAR) is:

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that
- Results in death
- Is life-threatening
- Required hospitalisation or prolongation of existing hospitalisation, excluding admission for birth or unrelated pregnancy condition
- Results in persistent or significant disability or incapacity
- Is otherwise considered medically significant by the principal investigator.

All AEs and SAEs must be recorded from the time a participant is randomized to treatment until 30 days after stopping taking study drug and until pregnancy outcome (28 days after delivery). The Investigator should ask about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant should be used to enquire about AE/SAE occurrence. Participants should also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE/SAE, the event should be recorded. Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. Complications occurring during such hospitalisation will be AE/SAEs.

Important Medical Events (IME): Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

9.5.3 Adverse events which do not require reporting

Expected serious adverse events (SAEs) are those events which are expected in the patient population or as a result of the routine care/treatment of a patient. The interventions they will be receiving are those which would be offered routinely in clinical practice. Cervical cerclage insertion is an established surgical procedure, which is associated with minimal risks. These

include infection, miscarriage, bleeding, difficulty with suture removal and preterm prelabour rupture of membranes.

Serious adverse events and serious adverse reactions (SARs) which are unrelated to these clinical procedures will be reported as SAEs.

Events that are primary or secondary outcome measures are not considered to be SAEs and will be reported in the normal way, on the appropriate electronic case report form.

Maternal:

- Premature labour
- Premature rupture of membranes
- Chorioamnionitis

Infant:

- Perinatal death (unless unexpected at this gestation)
- Low birth weight
- Requirement for supplemental oxygen or ventilation support
- Complications of prematurity (e.g. IVH, NEC, encephalopathy, seizures, hypoglycaemia) unless unexpected in this population
- Admission of the baby to the neonatal unit

In addition the following common pregnancy complication events will not be considered SAEs: hospitalisation for pre-eclampsia or pregnancy induced hypertension, hospitalisation for symptoms of preterm labour (e.g. rupture of membranes, vaginal bleeding); hospitalisation for maternal discomfort; hospitalisation for rest; hospitalisation for observation or monitoring for which the woman is admitted for a period of less than 12 h; delivery complications such as caesarean section or postpartum haemorrhage.

9.5.4 Reporting Responsibilities

All SAEs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the Investigator to the GSTT R&D Office and CI for review in accordance with the current Pharmacovigilance Policy. The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

The Chief Investigator (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) to the MHRA and REC annually.

9.6. Trial Management Group

Study management meetings will be held approximately every two months (with video conferencing where required). All researchers and clinicians affiliated with the project will be invited to participate in these meetings which will allow discussion of all aspects of the programme and the timely addressing of issues as they arise.

9.7. Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the study. The TSC will monitor the progress of the study and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether the trial needs to be stopped on the grounds of safety or efficacy. The TSC will consist of an independent chair and at least two other independent members (not involved in study recruitment and not employed by any organisation directly involved in study conduct. A representative from our dedicated preterm birth studies Patient Public Involvement group will be invited to participate. The first meeting will take place 6 months after trial start date; frequency will be decided at the first meeting (at least annually).

9.8. Data Monitoring Committee (DMC)

A DMC independent of the applicants and TSC will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC. The committee will periodically review study progress and outcomes. The timings and content of the DMC reviews will be detailed in a DMC charter which will be agreed at its first meeting. The DMC will meet 3 months following study commencement/recruitment of the first participant ; frequency of meeting will be decided at the first meeting.

9.9. Study Coordinating Centre

The trial coordinating centre will be the Department of Women and Children's Health, Kings College London, where the study coordinator will be based. The Division of Women's Health will be responsible for statistical analysis, servicing both the DMC and the Trial Steering Committee (TSC) and, in collaboration with the Principal Investigators, study coordinator and Local Research Midwives/Nurses, for the day to day running of the study including recruitment of sites and training of staff.

9.10. Trial stopping rules

The CRAFT-RCT trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the DMEC/TSC regulatory authority or ethics committee concerned. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

10. Investigator responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

10.1. Data Handling

All electronic data will be stored behind a secure firewall. Clinical information will be handled as appropriate for Trust patients to ensure maximum and efficient communication of results and clinical details to the appropriate clinical teams. Any patient identifiable data transferred from behind the firewall will be anonymised prior to transfer. This will only be used with authorised collaborators with explicit knowledge of how the data is being used.

The Principal Investigator is responsible for the quality of the data recorded in the electronic clinical research files. The Chief Investigator will act as custodian for the trial data. Patient data will be anonymised. All anonymised data will be stored on a password protected computer. All trial data will be stored in line with the Data Protection Act as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

10.2. Data Sharing

The Investigators will comply with the Kings College London (KCL) principles on data sharing and preservation. The consent form states that other researchers may wish to access (anonymised) data in future. The trial co-ordinator and statistician will (in collaboration with the CI) manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

10.3. Linkage of data

At the time of recruitment, a unique study number will be allocated to the patient. Only one copy of patent identifiable data linked to this number will be recorded on a password protected trust computer in order that recruits can be contacted and delivery outcomes recorded. The anonymised research record will not contain any patient identifiable data. All records will be anonymised at time of data entry in accordance with the General Data Protection Act 2018.

A bespoke internet-based data management system will be designed and built by RedCap and maintained by them. Varying levels of access are available from simple user to global administrator, each level requiring individual log-in and password. Minimal identifiers will be used on the main study database (initials, date of birth and unique study number). Contact details to ensure data completeness will be stored on a separate database linked only to study ID.

Paper copies of consent forms will be stored numerically (by study ID) and kept in a locked filing cabinet in accordance to the General Data Protection Act 2018 and EU GDPR directive. NHS numbers (mother and baby) will be collected to follow up pregnancy and neonatal outcomes for recruits who move away from study sites. NHS numbers will be held separately from main study data and only linked with study ID. Access to this information will be limited to specific study staff.

10.4. GCP Training

All study staff must hold valid GCP training certificates. This training will be updated every two years, or in accordance with local practice at collaborating sites, throughout the trial.

10.5. NHS Trust Research and Development

Individual sites will only start recruitment once they have received approval from their local NHS Trust Research and Development (R&D) offices. Applications to R&D offices will be submitted through the NIHR Co-ordinated System for gaining NHS permission.

10.6. Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Chief Investigator and the Co-Sponsors notified. Substantial amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

10.7. Protocol violations and deviations

The Investigator should not implement any deviation from the protocol except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator deviate deviation from the protocol, the nature of and reasons for the deviation should be recorded in the electronic clinical research files. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, Regulatory Authority and local R&D for review and approval by the Chief Investigator.

10.8. Direct access to source data and documents

Meetings will be held on a regular basis by the research team to monitor and audit the conduct of the research and review aspects of the CRAFT's study progress. The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, MRI reports etc).

11. Finance

Funding to conduct the CRAFT trial and imaging substudy is provided by J.P. Moulton Charitable Foundation (grant reference no. 261294). The trial will be registered on the CRN portfolio (JRM is an NIHR partner organisation) and will be supported by NIHR CRNs (IRAS no. 261294/CPMS no. 42833).

12. Publication Policy

Results of the study will be presented at national and international conferences and reported in peer reviewed journals. No patient identifiable information will be published. A lay summary will be available for participants via the study website.

13. Insurance and Indemnity

This study is co-sponsored by King's College London and Guy's and St Thomas NHS Foundation Trust. The sponsors will at all times maintain adequate insurance in relation to the study independently. King's College London, through its own professional indemnity (Clinical Trials) and no-fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient.

14.Signatures

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Chief Investigator Date:

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